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Predictive Genetic Testing for Breast and Prostate Cancer

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CCOHTA

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EXECUTIVE SUMMARY

This qualitative review describes the current molecular basis of breast and prostate cancer, assesses the clinical relevance of genetic susceptibility, addresses non-directive counseling, and explores the ethical, psycho-social, and policy implications associated with genetic testing.

Breast and prostate cancer are the second leading causes of death and the most frequently diagnosed malignancies in Canadian women and men, respectively. Age, ethnicity, and family history are definite risk factors for breast and prostate cancer. Hereditary breast and prostate cancers have been associated with alterations in the expression of tumor suppressor genes and oncogenes.

The majority of hereditary breast cancers can be attributed to germ-line mutations in the Breast Cancer susceptibility genes BRCA1 and BRCA2, with the remaining cases attributed to over-expression of oncogenes and other genetic aberrations. BRCA1 mutations have been shown to have greater prevalence in families in which there is presence of both breast and ovarian cancer. BRCA1-associated breast cancers are often of higher grade, over-expressing tumor suppressor protein 53 (p53), and are estrogen-receptor negative. In contrast to BRCA1, BRCA2 has been associated with fewer incident cases of ovarian cancer and several cases of male breast cancer. Two founder mutations in BRCA1 and one founder mutation in BRCA2, appear in about one-third of the breast cancer patients of Ashkenazi Jewish descent.

Protein expression of the oncogene Bcl-2 (B cell leukemia/lymphoma-2) and p53 have roles as independent prognostic markers for disease-free survival after radical treatment for prostate cancer. Predisposing mutations in the Hereditary Prostate Cancer 1 gene (HPC1) are responsible for only a minority of familial prostate cancer cases and they are likely to be most important in families of African-American origin and in families with at least four cases of the disease. Studies involving larger subsets of families should lead to the identification of further genetic susceptibility genes for prostate cancer, although by analogy with HPC1, the process is unlikely to be simple.

Key ethical implications arising from genetic testing for hereditary breast and prostate cancer include; informed consent, privacy and confidentiality, and familial implications. Significant psychological factors including stigmatization, lowered self-esteem, and anxiety are experienced by those of both carrier and non-carrier status. Predictive genetic testing for breast and prostate cancer has brought forth social issues such as the potential creation of a genetic subclass. Ethnic and gender issues compound the risk of genetic discrimination faced by carriers seeking insurance, employment, or adoption. Cost-utility data are required to assess the cost-effectiveness of genetic testing compared with conventional testing options for hereditary breast and prostate cancers.

Currently, genetic testing in Canada is only offered as part of clinical research programs that explore genetic testing as a potential component of routine medical care. As public awareness
and new technology develops, the pressure for greater genetic testing services is inevitable. Given the high public profile, vested private sector interest due to potential financial gain, and ethical, psycho-social, and policy implications associated with testing, it would be of benefit to establish clinical research guidelines for predictive genetic testing for families with significant family histories. For both breast and prostate cancer susceptibility, these guidelines could include: (i) a process for ensuring up-to-date information of the medical issues such as a standing panel comprising relevant disciplines; (ii) detailed training in cancer genetics for health care professionals who provide information and counseling in this area; (iii) the placement of genetic testing services in appropriate centres; (iv) non-directive counseling on the ethical, psycho-social, and policy issues; (v) the importance of obtaining informed consent; and (vi) encouraging individuals to participate in research.
SOMMAIRE

Les cancers du sein et de la prostate constituent la deuxième cause de mortalité et les tumeurs malignes les plus fréquemment diagnostiquées chez les Canadiennes et les Canadiens, respectivement. Dans ce domaine, l'âge, l'origine ethnique et les antécédents familiaux représentent des facteurs de risque certains. Selon la recherche, les cancers du sein et de la prostate héréditaires sont reliés à des altérations de l'expression d'oncogènes et de gènes suppresseurs de la transformation tumorale.

La majorité des cancers du sein héréditaires peuvent être imputés à des mutations dans les cellules germinales des gènes de susceptibilité BRCA1 et BRCA2 (BReast CAncer susceptibility genes), tandis que les autres cas sont attribuables à l'hyperexpression d'oncogènes et à d'autres aberrations génétiques. Il est démontré que la prévalence des mutations du gène de susceptibilité BRCA1 est plus élevé dans les familles où l'on observe à la fois des cas de cancer du sein et des cas de cancer ovarien. Les cancers du sein associés au gène BRCA1 sont souvent d'un degré de différenciation plus élevé, sont marqués par l'hyperexpression de la protéine suppresseur de tumeur p53 (protein 53) et sont à récepteur d'estrogène négatif. Comparé au gène BRCA1, le gène BRCA2 est lié à des cas de cancer ovarien moins nombreux, mais à plusieurs cas de cancer du sein chez l'homme. Deux mutations ponctuelles du gène BRCA1 et une mutation ponctuelle du gène BRCA2 sont mises en évidence chez environ le tiers des patientes de descendance juive ashkénaze atteintes du cancer du sein.

L'expression protéinique de l'oncogène Bcl-2 (B cell leukemia/lymphoma-2) et p53 jouent un rôle en tant qu'indicateurs de pronostic indépendants du taux de survie sans récidive à la suite du traitement radical du cancer de la prostate. Des mutations du gène HPC1 (Hereditary Prostate Cancer 1) suscitant la prédisposition ne sont responsables que d'une minorité de cas familiaux de cancer de la prostate, et elles sont probablement le plus déterminantes dans des familles d'origine afroaméricaine et dans des familles qui comptent au moins quatre cas de la maladie. Des études portant sur de vastes sous-groupes familiaux devraient permettre d'isoler d'autres gènes de susceptibilité du cancer de la prostate, bien que l'expérience avec le HPC1 laisse entrevoir que la démarche sera complexe.

L'examen génétique pour dépister les cancers du sein et de la prostate héréditaires soulève des questions d'éthique fondamentales, notamment celles du consentement éclairé et du respect de la vie privée et de la confidentialité, ainsi que des questions d'ordre familial. Par ailleurs, tant les porteurs que les non-porteurs subissent des effets psychologiques importants, tels la stigmatisation, la diminution de l'estime de soi et l'anxiété. En outre, l'examen génétique prédictif des cancers du sein et de la prostate a fait naître des questions d'ordre social, telles l'eugénisme. Des facteurs liés à l'origine ethnique et au sexe accroissent le risque de discrimination génétique que courent les porteurs désirant souscrire une assurance, recherchant un emploi ou entreprenant une démarche d'adoption. La collecte de données sur le rapport coût-utilité s'impose afin d'évaluer le rapport coût-efficacité de l'examen génétique par comparaison aux examens traditionnels en ce qui a trait aux cancers du sein et de la prostate héréditaires.
À l'heure actuelle au Canada, l'examen génétique ne s'effectue que dans le cadre de programmes de recherche clinique qui étudient son intégration possible aux soins médicaux courants. La sensibilisation accrue du public à ce propos et l'apparition de nouvelles technologies susciteront inévitablement une demande de services d'examen génétique. Étant donné la vive préoccupation du public pour cette question, les intérêts directs du secteur privé sur le plan financier et l'incidence éthique, psychosociale et politique de l'examen génétique, il serait judicieux d'établir des lignes directrices de recherche clinique en ce qui concerne l'examen génétique prédictif destiné aux familles dont les antécédents familiaux sont significatifs. Tant en ce qui a trait à la prédisposition au cancer du sein qu'à celle au cancer de la prostate, ces lignes directrices s'accompagneraient : (i) d'un mécanisme assurant la disponibilité de l'information la plus récente au sujet des aspects médicaux, tel un groupe permanent de professionnels des disciplines pertinentes; (ii) de la formation exhaustive dans le domaine de la génétique relative au cancer à l'intention des professionnels de la santé qui offrent de l'information et des services de counseling dans ce domaine; (iii) de la mise sur pied de services d'examen génétique dans des centres appropriés; (iv) du counseling non dirigé au sujet des questions d'ordre éthique, psychosocial et politique; (v) de l'importance d'obtenir le consentement éclairé des personnes en cause; (vi) de mesures incitant les personnes intéressées à participer à la recherche.
# TABLE OF CONTENTS

**REVIEWERS** ................................................................. i

**EXECUTIVE SUMMARY** .................................................. ii

**SOMMAIRE** ....................................................................... iv

1. **PURPOSE AND SCOPE** .................................................. 1

2. **BACKGROUND AND SIGNIFICANCE** ............................. 2
   2.1 Breast Cancer: *Synopsis of Appendix I* ......................... 2
   2.2 Prostate Cancer: *Synopsis of Appendix II* ....................... 3

3. **MOLECULAR GENETICS OF BREAST AND PROSTATE CANCER** .... 5
   3.1 Classification .......................................................... 5
      3.1.1 Sporadic, familial, and hereditary cancers ................... 5
      3.1.2 Genetic screening and genetic testing ....................... 5
   3.2 Family History and Genetic Risk Factors .......................... 6
      3.2.1 Breast cancer ................................................. 6
      3.2.2 Prostate cancer .............................................. 6
   3.3 Genetic Aberrations .................................................. 7
      3.3.1 Oncogenes ..................................................... 7
      3.3.2 p53 gene ..................................................... 9
      3.3.3 BRCA1 gene ............................................... 10
      3.3.4 BRCA2 gene ............................................... 14
      3.3.5 HPC1 gene ............................................... 14
      3.3.6 Other ..................................................... 15
      3.3.7 Summary .................................................. 17
   3.4 Hereditary Linkage of Breast and Prostate Cancer ............... 18

4. **CLINICAL RELEVANCE** .............................................. 19
   4.1 Predictive Ability of Current Detection Methods ................. 19
   4.2 Genetic Counseling ............................................... 23
      4.2.1 Pretest counseling ........................................... 23
      4.2.2 Post-test counseling ......................................... 25

5. **ETHICAL, PSYCHO-SOCIAL IMPLICATIONS** ......................... 27
   5.1 Ethical Issues ..................................................... 28
      5.1.1 Informed consent .......................................... 28
      5.1.2 Privacy and Confidentiality .................................. 30
   5.2 Psycho-Social Issues .............................................. 31


1. PURPOSE AND SCOPE

The following three objectives were identified for study:

1. describe the current state of knowledge on the molecular genetics of breast and prostate cancer;

2. assess the potential clinical relevance of genetic susceptibility to breast and prostate cancer;

3. examine ethical, psycho-social, and policy implications of genetic susceptibility to breast and prostate cancer given the availability of current and developing technologies.

This qualitative review describes the current molecular basis of disease, assesses the clinical relevance of genetic susceptibility, addresses non-directive counseling, and explores the ethical, psycho-social, and policy implications associated with genetic testing. Highlights on the background of the disease states, conventional screening and treatment options, and the clinical implications of genetic aberrations are summarized in the relevant sections.

The intended main audiences for this report are individuals at various levels of health care decision making. This review provides the information necessary to understand the scientific advances in these areas and to appreciate their broader implications when applied to clinical practice as a means of improving detection, treatment, and ultimately prevention of breast and prostate cancer.
2. BACKGROUND AND SIGNIFICANCE

2.1 Breast Cancer: Synopsis of Appendix 1

Breast cancer is the second leading cause of death due to cancer in Canadian women and the most common cancer to affect women. Each year in Canada an estimated 19,300 women are diagnosed with breast cancer and 5,300 women die of this malignancy. Overall, 1 in 9 women is expected to develop breast cancer during her lifetime, and 1 in 25 women is expected to die of breast cancer. In comparison to environmental factors, genetic factors confer greater increased risk of breast cancer for women whose first-degree relatives (mother, sister, or daughter) are affected by the disease. Although breast cancer is a disease which primarily affects women, approximately 1% of all new breast cancer cases are diagnosed in men.

Breast cancer is generally classified as invasive or non-invasive. Invasive cancer originates in the lobules and/or milk ducts, while non-invasive or in situ cancers are confined to the lining of the lobules or ducts. The most important criteria for assessing future risk of invasive disease is to determine whether cancer cells have invaded the lymph nodes. Breast cancer is commonly categorized into three grades according to growth rate. Well-differentiated tumors are termed as grade I; moderately differentiated tumors as grade II; and poorly differentiated tumors are termed as grade III. It is often difficult to differentiate between the various grade types under current conventional detection methods.

Breast cancer surveillance uses three standard methods: clinical breast examination (CBE), breast self-examination (BSE), and mammography. Examiner knowledge and experience are important factors when performing CBE, especially for discovering small breast lumps. For BSE to be effective, on the other hand, it must be implemented when the tumor is detectable and curable. The greatest reduction in mortality due to breast cancer occurs when diagnosis is made prior to the cancer developing into a lump or mass.

Screening mammograms are those performed when mammography is carried out in the absence of abnormal symptoms for the purpose of early cancer detection. If a screening mammogram indicates an abnormality, further high-quality mammograms are conducted to define the extent and location of the abnormality. Although studies suggest that screening mammography significantly reduces breast cancer mortality in women, its accuracy is dependent on several factors including breast density (age), imaging technique (single-view; two-view), and examiner knowledge. Health care professionals must consider both the individual’s risk status and the results of a CBE in order to determine whether it would be considerably difficult to interpret the results of a mammogram. Canadian clinics report significant differences in the timing and frequency by which they conduct mammogram surveillance, flagging the need to establish guidelines that are appropriate for high-risk women. Cost-effectiveness estimates for breast cancer surveillance depend on several variables including screening interval (annual versus biennial mammography) and rate of reduction in disease mortality.
When cytologic examination, mammography, and physical examination all indicate cancerous growth, a biopsy is conducted, and a small piece of breast tissue is removed and examined under a microscope noting any irregularities. Once the nature and extent of the tumor have been established by clinical and mammographic examination, a diagnosis of a clinical stage I or II breast cancer forms the basis for a treatment strategy comprising breast conserving surgery (BCS) followed by radiotherapy. Adjuvant chemotherapy is recommended for patients with advanced disease at diagnosis (clinical stage III and IV).

2.2 Prostate Cancer: Synopsis of Appendix 2

Prostate cancer is the second leading cause of male cancer deaths after lung cancer and is the most frequently diagnosed malignancy in Canadian men, with an estimated 4,300 deaths and 16,100 newly diagnosed cases in Canada in 1998. Furthermore, 1 in 8 Canadian men will develop prostate cancer during their lifetime while 1 in 26 will die of it. As with breast cancer, age, ethnicity, and family history are definite risk factors for prostate cancer. Prostate cancer represents 3.9% of the premature mortality caused by cancer in Canada.

Prostate cancer is a complex disease, both biologically and clinically. The clinical presentation of prostate cancer varies from small incidental carcinoma to aggressive metastatic disease, that is, it ranges from an indolent form that may never cause clinical symptoms to an aggressive form that is commonly fatal. For prognostic purposes, as with breast cancer, the histological results are usually categorized into three grades. Once a diagnosis has been established, treatment often depends on clinical and pathologic staging.

Conventional screening methods for prostate cancer are digital rectal examination (DRE) and measurement of prostate specific antigen (PSA). These tests are useful in deciding whether a TRUS (transrectal ultrasound-guided) biopsy of the prostate is indicated or not. The DRE has been the physician’s primary screening tool during routine health examinations; however, its true sensitivity and specificity remain unknown due to a lack of both uniformly performed biopsies and long-term follow-up of the screened population in published studies. The inability of DRE to detect tumors in the anterior and medial lobes of the prostate, and inter-examiner variability, limit its relative sensitivity as a screening test for prostate cancer.

Measurement of serum PSA is currently the most sensitive non-invasive screening test for prostate cancer. The odds of detecting both clinically significant prostate cancer or early-stage disease are generally higher with PSA measurement as compared to DRE. PSA, however, provides both a lead time bias, and a length time bias. Cost-effectiveness analyses of screening for prostate cancer with DRE and PSA are difficult to interpret given the different model structures between studies, context, and timing adopted for analysis. Controversy exists regarding recommendation for or against the use of PSA as a routine screening test in the absence of randomized-trial data on screening for prostate cancer.
Treatment choice for prostate cancer depends primarily on the stage of disease at diagnosis; the histological grade, patient’s age, and general health are also considered. For men with cancer apparently confined within the prostatic capsule showing no clinical evidence of nodal involvement or metastases, the alternative treatment options are (i) expectant management, delaying radical or systemic treatment until the cancer shows sign of progression, (ii) radical prostatectomy, and (iii) radical radiotherapy. Hormonal therapy is often the first line of treatment for lymph-node or disseminated metastases either on initial diagnosis or when presented as a relapse from failed local therapy. No precise clinical or economic comparisons between treatment modalities are possible to date in the absence of data from well-designed randomized prospective trials.
3. MOLECULAR GENETICS OF BREAST AND PROSTATE CANCER

3.1 Classification

3.1.1 Sporadic, familial, and hereditary cancers

Most genetic changes arise spontaneously (sporadic mutations) and are not inherited from either parent.\(^1\) Familial and hereditary are terms that refer to increased cancer risk within families; however, they are not synonyms.\(^2\) Familial cancer is defined as the simple clustering of disease within families, for example, when two brothers have prostate cancer.\(^3\) Hereditary cancer is a more specific term, referring to a subtype of familial disease with a pattern of distribution consistent with Mendelian inheritance of a susceptibility gene. The etiology of familial disease involves a variety of mechanisms, including familial exposure to environmental or dietary risk factors, several genes whose absence or new presence working together contributes to polygenic inheritance, or even chance alone. Conversely, the etiology of hereditary disease most likely results from the loss or inactivation of a single gene passed along in families that confers increased susceptibility for the development of cancer.

Hereditary breast cancer is clinically distinct from sporadic cases in that the age of onset is considerably younger, the prevalence of bilateral affliction is higher, and there is a greater presence of associated tumors in affected individuals. In contrast, sporadic cancers generally occur later in life as a single tumor. Histology, morphology, metastatic pattern, and survival characteristics are similar regardless of whether the case is sporadic or inherited. Consistent with Mendelian transmission of autosomal dominant inheritance, hereditary breast cancer is defined when a woman has two or more first degree relatives (mother, sister, or daughter) who have been diagnosed with the disease. The lifetime risk of developing breast cancer for a woman whose mother or sister had bilateral disease is 25%; if her mother or sister had unilateral disease, her risk is about 15%; whereas the general population risk is approximately 7%.\(^4\) For prostate cancer, approximately 25% of all men have a known family history; however, only 9% have a hereditary form of the disease. The criteria for diagnosis of hereditary prostate cancer are that there are more than three affected family members, and that it occurs in three successive generations or that two family members have developed the disease before 55 years of age.\(^5\)

3.1.2 Genetic screening and genetic testing

Genetic tests include the many different laboratory assays used to diagnose or predict a genetic condition or the susceptibility to a genetic disease.\(^1\) Genetic screening involves the use of various genetic tests to evaluate populations or groups of individuals independent of a family history of a disorder. Genetic testing, on the other hand, denotes the use of specific assays to determine the genetic status of individuals already suspected to be at high risk for a particular inherited condition because of family history. For this report, genetic testing will also denote the use of
tests to determine the genetic status in ethnic groups expressing high prevalence of specific types of mutations (for example, founder mutations) susceptible for disease.

3.2 Family History and Genetic Risk Factors

3.2.1 Breast cancer

Familial clustering of breast cancer was initially documented in 1886 by a French surgeon, Paul Broca. Tracing his wife’s family through five generations, Broca noted that 10 (of 24) of the women had died of breast cancer. This finding suggested that chance was not the solitary factor involved in developing the disease. A common feature of heritable breast cancer is the occurrence of families in which malignancy is diagnosed early in life. Genetic epidemiological studies using segregation analysis suggest that these pedigrees (a diagram setting forth the ancestral history or genealogical register) frequently reflect the phenotypic effect of single autosomal dominant genes. These genes are carried in 1 to 6 (of every 1000) individuals and give a greater than 80% lifetime risk of breast cancer, with a 40% risk prior to age 50. The population frequency of hereditary breast cancer based on segregation analysis is 0.33%. It is estimated that 1 in every 150 women bears a predisposition to hereditary breast cancer.

Genetic linkage analysis (section 3.1) of 23 extended families by Hall et al. (1990) has demonstrated linkage between early-onset breast cancer and a genetic marker mapping to the long arm (q) of chromosome 17, subsequently termed BRCA1 gene 1 (BRCA1). Further reports have provided evidence for the co-transmission of breast and ovarian cancer susceptibility, and confirmed the results of linkage between breast cancer and genetic markers on 17q. Chamberlain et al. (1993), moreover, were the first to demonstrate linkage of breast cancer to genetic markers on this region in a family of African-American descent.

In 1994, a candidate gene for BRCA1, which was responsible for an inherited predisposition to breast and ovarian cancers was isolated by positional cloning. This gene appears to account for the majority of families segregating early-onset breast and ovarian cancer, but only a minority of families segregating breast cancer only. Wooster et al. (1994) demonstrated that a significant proportion of such families where the disease was not attributed to BRCA1 were linked to a gene on chromosome 13q (band 12-13), later cloned partially and completely and termed as BRCA2.

3.2.2 Prostate cancer

Credit for the awareness of prostate cancer as a familial disease goes to the Utah Mormon population in the United States. This is due to the availability of extensive genealogical records providing a unique resource for the study of familial factors in various cancers. Several case-control studies have provided strong evidence of familial clustering of prostate cancer. As shown in the Steinberg et al (1990) study, the nature of this clustering is a trend of increasing risk
of developing prostate cancer with increasing numbers of affected family members. Men with 2 or 3 first-degree relatives with prostate cancer had a 5- and 11-fold increased risk of developing this malignancy, respectively.

Carter et al. (1992) were the first to report that this familial clustering is best explained by an autosomal dominant gene. Using segregation analysis in 691 prostate cancer families, they identified a rare allele (q=0.0030) which results in early onset of prostate cancer (mean age of diagnosis of 59.3 years). This allele was highly penetrant, with 88% of the gene carriers predicted to develop disease by the age of 85 years. They concluded that this inherited form of prostate cancer accounts for a significant proportion (43%) of early onset disease (<55 years), although it is responsible for only about 9% of all cases of prostate cancer diagnosed by age 85 years. A segregation analysis by Gronberg et al., performed on a population-based sample of 2,857 prostate cancer families in Sweden, confirmed this dominant mode of transmission. However, the lifetime penetrance was lower (63%) and the gene frequency significantly higher (q=0.0167) than that observed by Carter et al (1992).

Variability in selection of the study populations and involvement of multiple genes in the inheritance of this complex disease might explain the differences between the above segregation analyses. Further evidence of the genetic heterogeneity for hereditary prostate cancer has been provided by Schaid et al. (1998) in a recent segregation analysis conducted on 5,846 men undergoing radical prostatectomy in the USA for clinically localized disease. The model by Schaid et al. (1998) predicted an intermediate gene frequency for the population (.006) with the risk of prostate cancer by age 85 years being 89% among carriers of the gene, and 3% among non-carriers. The best-fitting model that explains the familial aggregation and age at diagnosis for this disease in the latter analysis are in keeping with the above findings by Carter et al (1992) -that is the presence of a rare autosomal dominant susceptibility gene, in individuals with an early onset of disease (diagnosed at <60 years of age).

### 3.3 Genetic Aberrations

#### 3.3.1 Oncogenes

Oncogenes are derived from cellular genes (proto-oncogenes) which are either mutated or inappropriately expressed. Over-expression due to gene amplification or mutations in regulatory sequences lead to alterations in cellular proliferation, differentiation, and homeostasis. For example, while the majority of cases for hereditary breast cancer can be attributed to germ line mutations in one of two tumor suppressor genes, BRCA1 and BRCA2, evidence suggests oncogenes, along with other susceptibility genes, contribute to the remaining number of cases. Three classes of oncogenes implicated in breast and prostate cancer are growth factor/hormone receptors, signal transducers, and nuclear factors. At present, however, no single oncogene has been shown to play a clearly defined role in the development of either malignancy.
Growth factor/Hormone receptors: The epidermal growth factor receptor family is implicated in the pathogenesis of both breast and prostate cancers. c-erbB-2, neu, and HER2 are all names for the same gene that was identified initially in 1981 from a rat neuroglioblastoma. This gene (hereafter referred to as HER2) was identified in human tumor tissue by two independent groups in 1985. HER2 is located on chromosome 17q21-22 and codes for a protein that is similar to the epidermal growth factor receptor. HER2 has been shown to be over-expressed in a subset of both breast and prostate cancer families. For example, in lymph node positive or node negative breast cancer patients, there is a strong correlation between HER2 amplification and poor prognosis although the evidence that HER2 promotes metastasis is controversial. HER2 has also been linked to resistance to hormonal therapy and chemotherapeutic strategies involving cyclophosphamide, methotrexate, fluorouracil, and anthracyclines.

The insulin-like growth factor-1 receptor (IGF-1) is expressed in both breast and prostate cancers, and its expression has been associated with poor prognosis. For breast cancer, IGF-1 has been shown to influence the effect of anticancer agents; it increases the cell survival of breast cancer cells treated with tamoxifen, 5-fluorouracil, methotrexate, camptothecin and serum withdrawal. This finding suggests that a search is required for drugs that lower IGF-1 to improve the efficacy of chemotherapeutic drugs used to treat breast cancer.

A prospective case-control study of men (152 cases and 152 controls) participating in the Physicians’ Health Study (a randomized, double-blinded, placebo controlled trial of ß-carotene and aspirin in U.S. male physicians aged 40 to 82 without prior diagnosed cardiovascular disease or cancer) revealed a 4-fold increased risk of developing prostate cancer among men with the highest levels of IGF-1 compared to men who had the lowest IGF-1 levels. Given the small number of study subjects, the relationship between IGF-1 and prostate cancer is not clear to date.

Signal Transducers: The ras (rat sarcomas) genes encode proteins known as p21 proteins, the so-called signal transduction proteins which transfer information from outside the cell to the cell nucleus. Ras has also been shown to be over-expressed in breast tumors. Ras over-expression has been associated with a poor prognosis, and its interaction in the signal transduction pathway involving other oncogenes, namely HER2, has been noted. For prostate cancer, interestingly, there is a suggestion (from two studies of the Japanese male population) that ethnic and/or racial differences may exist in relation to ras mutation frequency. However, as with findings with other candidate oncogenes, additional work among a variety of populations will be necessary to provide definitive information regarding this subject.

Nuclear Factors: Activation and over-expression of the myc (myelocytomatosis) family of oncogenes, particularly c-myc, has also received attention regarding a possible role in both breast and prostate cancers. c-Myc is one of the most frequently amplified genes in human breast cancer, demonstrating a 2- to 15- fold amplification in approximately 30% of carcinomas. c-Myc expression has been demonstrated to be an independent prognostic indicator in breast cancer; over-expression of which correlates with high tumor grade, lymph node metastasis, and
early and intermediate risk of relapse.\textsuperscript{40} The question of whether \textit{c-myc} will be a clinically useful tumor prognostic marker for prostate cancer is still unsettled.\textsuperscript{27}

The \textit{Bcl-2} (\textit{B} cell \textit{leukemia/lymphoma-2}) family of genes (\textit{Bcl-2}, \textit{Bax}, \textit{Bclx}) are involved in maintaining balance between cell proliferation and programmed cell death.\textsuperscript{26} \textit{Bax} counteracts the cell survival effect of the \textit{Bcl-2} gene. While relatively similar expression is observed in normal and benign tissue, differential expression is observed in malignant tissue according to tumor stage and development. For breast cancer, \textit{Bcl-2} is predominantly expressed in well-differentiated DCIS (ductal carcinoma in situ)\textsuperscript{41} and has been strongly correlated with estrogen-receptor (ER)- positivity and smaller tumor size.\textsuperscript{42} In contrast, \textit{Bax} protein is primarily expressed in poorly differentiated DCIS. Moderately differentiated lesions display co-expression of both \textit{Bcl-2} and \textit{Bax}. Over-expression of \textit{Bclx} protein has also been associated with higher tumor grade, increased number of positive nodes, and a trend toward decreased overall patient survival.\textsuperscript{42} In summary, \textit{Bax} and \textit{Bclx} protein expression, especially in DCIS, correlates with more aggressive neoplasms, while \textit{Bcl-2} protein expression is associated with less aggressive malignancy.\textsuperscript{41}

Unlike its role in breast cancer, \textit{Bcl-2} has been implicated in cancer progression and androgen-independent prostate disease in the recent literature.\textsuperscript{43-45} For example, a study by McDonnell et al. (1992) showed a strong correlation between \textit{Bcl-2} over-expression and progression of androgen-dependence to hormone-resistance in prostate cancer.\textsuperscript{43} This effect has recently been shown to be more pronounced when \textit{Bcl-2} over-expression was combined with \textit{p53} nuclear protein accumulation.\textsuperscript{46} In addition, patients with over-expression of \textit{Bcl-2} in their tumors have been shown to have a significantly higher 5-year failure rate (tumor recurrence) than those who do not over-express \textit{Bcl-2}.\textsuperscript{44} This latter finding suggests that \textit{Bcl-2} may also play a role as a biomarker to predict recurrence after radical prostatectomy in patients with clinically localized prostate cancer.

3.3.2 \textit{p53} gene

The \textit{p53} tumor suppressor gene, located on the short arm (\textit{p}) of chromosome 17 (17\textit{p}, band 13), has been extensively studied. Mutations in this gene have been documented in a large variety of human cancers.\textsuperscript{47-49}

Germ-line mutations in \textit{p53} have been described in rare cancer-prone families with Li-Fraumeni syndrome.\textsuperscript{50-52} Segregation analysis demonstrates that cancer distribution in families with Li-Fraumeni syndrome fit an autosomal dominant inheritance pattern. These families show a high incidence of soft-tissue sarcoma, bone, brain, lung, laryngeal, adrenal, and pre-menopausal breast cancers, in addition to leukemia.\textsuperscript{53} Breast cancer in families with Li-Fraumeni syndrome account for approximately 1\% or less of all inherited breast cancers.\textsuperscript{53}

Mutant \textit{p53} expression has been implicated in both inherited and sporadic cases of breast cancer, and has been used as a parameter to evaluate the cellular biology and prognosis of DCIS.\textsuperscript{54, 55} \textit{p53}
protein expression may identify cases of DCIS which are more likely to progress to invasive carcinoma; therefore used as a marker, p53 expression may influence management and treatment strategies.56

Mutations of p53 have also been demonstrated to date in three (of five) prostate cancer cell lines, and the growth of these lines is suppressed by the introduction of a wild-type (normal) copy of this gene.57 Mutations in primary prostate tumors appear to occur at a low frequency (10 to 20%) compared to other cancers,58, 59 although some controversy exists with respect to this estimate depending on the method of analysis (immunohistochemical or molecular).60, 61 In studies of advanced disease, the incidence of p53 mutations has been shown to be more common in later stage tumors58, 59, 61 and androgen-independent tumors,59 inferring that altered p53 is important in the progression of human prostate cancer and such mutations may signify transition to hormone-refractory disease. However, others have shown that p53 abnormalities are also a feature of a subset of early stage disease62, 60 and of precursor lesions.63 The above inference is, therefore, called into question, and it remains to be seen whether p53 mutations are truly indicative of aggressive clinical behavior.

As with the case of breast cancer, recent studies have shown that p53 expression may influence the management and treatment of prostate cancer. Two studies by Bauer et al. (1995; 1996), for example, have shown that in radical prostatectomy specimens mutant p53 expression was found in 65% (114 of 175) of patients. Using immunohistochemical staining the investigators observed that these patients had a significantly higher 5-year failure rate of tumor recurrence (51%), as compared with a 5-year failure rate of 22% in p53-negative patients.64, 44 This finding was independent of age, race, stage, and grade. When p53 staining was combined with Bcl-2 overexpression, the 5-year failure rate was 75%. Conversely, when both p53 and Bcl-2 staining were negative the 5-year failure rate was 20%.44 Moreover, a recent study by Prendergast et al. (1996), has demonstrated that p53 abnormalities occur at a high incidence (72%) in resected prostatic carcinoma specimens following local failure after radiotherapy.65 Although these studies need to be confirmed by other groups of investigators, it appears that p53 may be an important biomarker to predict recurrence in clinically localized prostate cancer patients after both radical prostatectomy and radiotherapy.

3.3.3 BRCA1 gene

Following extensive linkage, mutational analysis, and physical mapping of DNA (deoxyribonucleic acid) within the long arm of chromosome 17, the tumor suppressor (breast cancer susceptibility) gene number 1 (BRCA1, 17q21) was discovered to confer a predisposition to breast cancer.13 The contribution of BRCA1 and BRCA2 to inherited breast cancer has been assessed (International Breast Cancer Linkage Consortium) by linkage and mutation analysis in 237 families, each with at least four cases of breast cancer without regard to the occurrence of ovarian and other cancers.24 Overall, disease was linked to BRCA1 in an estimated 52% of families, to BRCA2 in 32% of families, and to neither gene in 16%. The majority (81%) of the breast-ovarian cancer families were due to BRCA1, with most others (14%) due to BRCA2.
Conversely, the majority of families with male and female breast cancer were due to BRCA2 (76%). The largest proportion (67%) of families due to other genes was found in families with four or five cases of female breast cancer only. However, recent analyses suggest that the actual prevalence of BRCA1 mutations in high risk families might be much lower and may be influenced by age of onset of the breast cancer, family history, ethnicity and the presence of ovarian cancer.

In a study of breast cancer cases and controls, a gene frequency of 0.003 (carrier frequency of 1 in 152) was derived for gene(s) conferring susceptibility to breast cancer. An English study based on families of patients with breast or ovarian cancer revealed a gene frequency of 0.0006 (carrier frequency of 1 in 833). It will be essential to test by direct measurement of mutations in the general population. This is especially important for the French Canadian population for which estimated frequencies obtained from other populations cannot be extrapolated due to the major impact of founder effect in French Canadians.

In general, approximately 1 in 500 women is a BRCA1 mutation carrier. By the age of 70, BRCA1 mutation carriers have a 56-87% risk of acquiring breast cancer and approximately a 16-44% chance of developing ovarian cancer. The US Breast Cancer Linkage Consortium data from BRCA1-linked families provides evidence for two patterns of risk inheritance. By the age of 60, one common allele confers a breast cancer risk of 62% and an ovarian cancer risk of 11%; the other confers a risk of 39% for breast cancer and 42% for ovarian cancer. Loss of heterozygosity (LOH) analysis indicates that somatic mutations in BRCA1 also play a minimal role in some sporadic cases of breast cancer. Although the absence of mutations in the BRCA1 gene in sporadic mammary tumors is rather puzzling, the role of BRCA1 in these cancers is suggested by its 5- to 10-fold higher expression in normal mammary cells compared to invasive breast cancer cells.

The BRCA1 gene comprises 5,592 nucleotides, in which 22 exons encode a protein of 1,863 amino acids in length, with a DNA binding motif near the amino terminus. An important feature of the in vivo pattern of BRCA1 and BRCA2 expression is that each of these tumor suppressor genes is expressed at maximal levels in rapidly proliferating cells and their expression is essential for early embryonic proliferation and development in animal models. Their expression and phosphorylation are coordinated and up-regulated in a cell cycle-dependent manner, peaking at the G1/S boundary. Both BRCA1 and BRCA2 can interact with Rad51, a major participant in eukaryotic double-stranded break repair, thus strongly suggesting their involvement in the maintenance of genome integrity. Alterations in BRCA1 result in the production of an ineffective protein from that allele and consequently may lead to unregulated cell proliferation. This gene has been associated with mutations that segregate with breast and ovarian cancer in linked families. BRCA1 has been extensively analyzed for mutations which appear to be spread over the entire gene.
It has been postulated that \( p53 \) mutation is required for \( BRCA1 \) tumorigenesis. The pivotal role of \( p53 \) has been suggested by two studies which indicate a high frequency of \( p53 \) over-expression in a high proportion of \( BRCA1 \)-associated breast cancers. Crook et al. (1997) suggest that \( p53 \) mutation is responsible for the increased cellular proliferation observed in \( BRCA1 \)-associated breast cancers.\(^8\) However, the results of Eisinger et al. (1997) suggest that when comparing \( BRCA1 \)-associated disease with sporadic cases, tumor proliferation is not solely dependent upon control by \( p53 \), but also by \( BRCA1 \)-germline mutation.\(^8\) Despite the frequency of \( p53 \) being positively equivalent to that of \( BRCA1 \)-associated cancers (70%), only 46% of hereditary non-\( BRCA1 \) breast cancers are associated with a high cellular proliferation rate when compared to that of \( BRCA1 \)-associated breast cancer. Thus, it appears that \( p53 \) involvement is likely to be an additional event, as opposed to a mandatory checkpoint in the development of hereditary breast cancer. Analysis of the interrelations between \( p53 \) alterations and prognosis of \( BRCA1 \)-associated breast cancer offers promising implications for management. For example, those who have a \( BRCA1 \)-associated medullary carcinoma of the breast have been observed to frequently harbor a mutation in \( p53 \), and generally have a better prognosis than other grade-3 ductal carcinomas.\(^8\)

Recurrent mutations appear to be prominent in some Canadian families. For instance, 4 (of 12) families that contain \( BRCA1 \) mutations had an insertion of cytosine following nucleotide 5382 (5382insC), and another four families displayed a deletion of an adenine and guanine in nucleotide position 185 (185delAG). All families with the same mutation inherited the same alleles at three markers lying within \( BRCA1 \).\(^8\) This is promising in that it indicates that there may be a manageable number of founder chromosomes to account for \( BRCA1 \) mutations, and that mutation prediction rather than detection may be feasible using haplotype analysis.\(^8\) Founder effects and linkage disequilibrium are likely to be more prevalent within well-defined ethnic groups. The ability to demonstrate diversity in mutation-haplotype patterns between ethnic groups may confer advantages over an ordered mutation search throughout the \( BRCA1 \) gene.\(^8\) For example, while several hundreds of mutations have been identified within the \( BRCA1 \) gene, two mutations, 185delAG and 5382insC, along with the 6174delT (thymidine) mutation in \( BRCA2 \), account for a considerable percentage of breast cancer cases in the North American Ashkenazi Jewish population.\(^7, 8, 9\)

The above founder mutations 185delAG and 5382insC in \( BRCA1 \), and 6174delT in \( BRCA2 \), appear in 60% of ovarian cancer and 30% of early onset breast cancer patients of Ashkenazi Jewish descent.\(^9\) However, penetrance of \( BRCA1 \) 185delAG and 5382insC was found to be significantly higher than that of \( BRCA2 \) 6174delT.\(^9\) Approximately 2.4% of the North American Ashkenazi Jewish population is thought to carry mutations in these genes, causing these mutations to be 10 times more prevalent in this ethnic group than in the population as a whole.

The number and type of \( BRCA1 \) and \( BRCA2 \) mutations can vary significantly between populations. Although an ethnic group may display greater prevalence of a particular mutation, this does not mean to say that this population holds a correspondingly high incidence of breast cancer. For example, although the North American Ashkenazi Jewish population appears to have a significantly higher number of individuals with alterations in \( BRCA1 \) and \( BRCA2 \), the rate
of breast cancer incidences in the Ashkenazi Jewish population is not 10 times greater than that of other populations. Two mutations in BRCA1, 5382insC and 4153delA, were ranked far more common in high-risk Russian families than elsewhere, occurring in 79% of families at high-risk for breast or ovarian cancer. Israel ranked second highest, with 47% of high-risk families carrying specific mutations in BRCA1. Due to the relatively small number of founding populations in Israel, in comparison with other countries, two specific mutations appear to account for most of the BRCA1 mutations.

The BRCA1 mutation (2804delAA) was estimated to have originated 32 generations ago and is founded in Dutch and Belgian hereditary breast and ovarian cancer families. Four Swedish founder mutations have been identified as 2595delA, C1806T, 3166insTGAGA, and 1201del11, most of which manifest a predominantly ovarian cancer phenotype. The 999del5 BRCA2 mutation founded in Icelandic breast cancer families was noted to occur in 7.7% of female breast cancer patients, and 40% of males with breast cancer. The latter mutation was strongly associated with onset of female breast cancer prior to age 50, suggesting a possible contribution of an environmental factor. This particular recurrent mutation, 999del5 in BRCA2, has also been recently noted in a Finnish breast cancer population. Women of the Zoroastrian faith (a Parsi ethnic group) living in areas around metropolitan Mumbai, India, have been reported to have a significantly high incidence of breast cancer. Over 60% of the Parsi breast tumors are shown to harbor alterations in p53, a figure higher than that observed in other communities. Other populations which appear to contain founding mutations not prevalent elsewhere in the world include those of Britain, Italy, France, Germany, Hungary, and Canada. As a result of migration, the mosaic nature of populations in Canada and the United States make mutation detection in these countries technically challenging.

BRCA1 carriers have been observed to display significantly lower birth weight and length, and are smaller at gestational age than non-carriers, suggesting that BRCA1 mutations influence development in utero. However, mammographic appearance of the breast and breast cancer in BRCA1 carriers has been shown to be similar to that in the general population, making appropriate management of high-risk individuals yet to be determined. In contrast to expectations, clinical implications of BRCA1 genetic testing, both positive predictive value for those with BRCA1 mutation and negative predictive value for those without the mutation, have been difficult to establish. Based on pedigree analysis and genetic testing in a patient with familial breast or breast-ovarian cancer, the predictive value of carrier status ranged from the possibility of multiple cancers and death at a young adult age, as well as the possibility of living healthly for more than 70 years. It was impossible to determine the predictive value of not carrying the mutation because other disease-associated mutations may segregate in the family. True anticipation beyond ascertainment bias has not been demonstrated in BRCA1 families. BRCA1-associated breast cancers are often of grade III, highly proliferating, with p53 over-expression and are ER-negative.

Evidence for a genotype-phenotype correlation suggests that truncation of conserved terminal regions of the BRCA1 protein is associated with highly proliferating hereditary breast cancers.
*BRCA1* has recently been shown to play a role in cis-diamine-dichloro-platinum II resistance in breast and ovarian cancer cell lines. However, despite indications of a poor prognosis, overall survival of *BRCA1* carriers is equivalent to sporadic cases. Survival rates among individuals with breast and ovarian cancer in *BRCA1*-linked families in Sweden concluded that survival in *BRCA1* mutation carriers is similar to, or worse than, that for breast and ovarian cancer patients in general. The studies to date contain a relatively small number of *BRCA1* cases and possibly age-mismatched controls, giving rise to conflicting results. Further studies are required to overcome limitations in research design and provide a more accurate estimate of survival rates of *BRCA1* breast and ovarian cancer patients. The discrepancy between indicators of poor prognosis and the lack of decreased survival in carriers might be accounted for in part by the finding that *BRCA1*-associated breast cancers display a low frequency of axillary lymph-node involvement in comparison with controls. Lymph-node involvement reflects the metastatic capacity of the tumor, implying that the relation between these elements is different in sporadic and hereditary cases.

### 3.3.4 *BRCA2* gene

The majority of the remainder of the genetic risk for breast cancer is attributed to the breast cancer susceptibility gene number 2 (*BRCA2*), located on chromosome 13q (band 12-13), as identified by Wooster et al. *BRCA1* and *BRCA2* together account for approximately 80% of all hereditary breast cancer cases. In contrast to *BRCA1*, *BRCA2* is associated with several cases of male breast cancer and very few incident cases of ovarian cancer, although this division is no longer as clear as originally thought. While breast cancer has generally been considered a woman’s disease, men may also develop the disease as they too have breast tissue. Breast cancer accounts for about 1% of all cancers in men, and approximately 0.5% of all breast cancer cases occur in men. The cumulative risk of breast cancer in female *BRCA2* gene carriers is estimated to be 59.8% by age 50, and 79.5% by age 70, while that for male carriers is 6.3% by age 70. Compared to breast cancer, ovarian cancer incidence is less common in the general population; therefore, absence of ovarian cancer in a *BRCA1*-linked family may be due only to chance. Similarly, the occurrence of male breast cancer in a pedigree may be suggestive of *BRCA2* rather than *BRCA1*-linkage, however, the possibility of *BRCA1*-linkage cannot be ruled out.

Genetic linkage analysis suggests that further genes conferring predisposition to breast cancer are yet to be discovered. For example, another candidate gene, *BRCA3*, has been localized on chromosome 8 (p12-13). Recent analysis suggests that very few family cancers are linked to this region.

### 3.3.5 *HPC1* gene

Smith et al. (1996) undertook linkage analysis on 79 North American and 12 Swedish families, each having at least three first-degree relatives with prostate cancer. A genome-wide scan performed with 341 polymorphic markers in a subgroup of 66 North American families, found evidence of linkage to the long arm of chromosome 1 (1q, band 24-25). Analysis of an
additional 25 families and markers in this region strengthened the case for linkage. There was
evidence of linkage in Swedish and North American Caucasian families as well as in African-
American families, suggesting that this locus exists in a variety of populations and ethnic
backgrounds. An estimated 34% of familial cases were linked to the 1q24-25 region. Smith et
al. (1996) proposed the designation of \textit{HPC1} (\textit{h}ereditary \textit{p}rostate \textit{c}ancer \textit{1}) for this genetic locus. This
finding brought about direct evidence that an inherited change can lead to prostate cancer.

Two subsequent studies confirm this disease linkage to \textit{HPC1}.\textsuperscript{125,126} Three clinically important
differences have been observed between potentially linked families for \textit{HPC1} in comparison with
potentially unlinked families, based on haplotype analysis: a younger age at diagnosis, higher
tumor grade, and more advanced-stage disease in \textit{HPC1} case patients.\textsuperscript{126}

Confirmation of this linkage to \textit{HPC1} in further independent data sets is essential given
especially the reported results by Eeles et al. (1998) who found no evidence for linkage of
prostate cancer to 1q24-25.\textsuperscript{127} Analysis by both parametric (based on the model suggested by
Carter et al. (1992)\textsuperscript{5}) and nonparametric methods failed to confirm linkage to this region in 136
multi-national prostate cancer families.\textsuperscript{127} Such conflicting evidence between studies regarding
estimates of the proportion of families with prostate cancer linked to the \textit{HPC1} region may be
explained by a multitude of generic reasons, including a false-positive or false-negative result
and/or study-population differences in the presence of locus heterogeneity. For example, the data
set of Smith et al. (1996)\textsuperscript{124} contained two African-American families that contributed
approximately one-half of the \textit{lod} (logarithm of the odds) score for the North American pedigrees
studied, whereas the data set of Eeles et al. (1998)\textsuperscript{127} contained no African-American families.
This difference is significant given the higher morbidity and mortality reported for prostate
cancer in African-Americans compared to other racial/ethnic groups. A more important factor
that might explain this discrepancy between the above results is the number of prostate cancer
cases in a family: 73% of the families in the analysis by Eeles et al. (1998) included \#3 affected
cases, whereas the average number of affected cases in Smith’s analysis was 4.9 (range 3-15).\textsuperscript{124}

The identification of prostate cancer families should lead to the identification of further genetic
susceptibility genes,\textsuperscript{128} although by analogy with \textit{HPC1}, the process is unlikely to be simple.

\textbf{3.3.6 Other}

\textbf{ATM gene and Breast Cancer:} The ataxia-telangiectasia gene, \textit{ATM} (mutated in A-T), a gene
which confers sensitivity to radiation, is a strong candidate for modifying cancer susceptibility.
Ataxia-telangiectasia, A-T, is a multi-system recessive disease characterized clinically by
cerebellar degeneration, oculo-cutaneous telangiectasias, immunodeficiency, sensitivity to radio-
mimetic agents, and cancer predisposition. Using genetic linkage analysis, the disease locus was
mapped to chromosomal region 11q (band 22-23). The \textit{ATM} gene protein is implicated in
regulating cell cycle and response to DNA damage. The risk of breast cancer in patients with A-
T is about 5 times greater than the non-A-T population.\textsuperscript{129} Since A-T heterozygotes constitute
approximately 0.2-1\% of the general population, a significant fraction of breast carcinomas may
develop in A-T allele carriers. Assuming a disease gene frequency of 0.005 and a relative risk of 3.9, an estimated 3.8% of breast cancers may develop in A-T allele carriers.\textsuperscript{130}

Prevention programs involving routine mammographic screening as a diagnostic procedure may be inappropriate for A-T patients, as doses of ionizing radiation at or above 20 mGy have been demonstrated to induce breast cancer A-T heterozygotes.\textsuperscript{131} The rate of breast cancer incidence for first-degree relatives of families affected by A-T are 0.29% for those aged 40-49 years; 0.71% in women aged 50-59; and 0.61% for those aged 60-69 years of age. For women older than 70 years, the incidence of occurrence decreases to 0.54%. The benefit of mammography in terms of reducing breast cancer mortality must be weighted against the risk of inducing breast cancer by exposure to the accumulated screening radiation dose in A-T heterozygotes.\textsuperscript{132}

**AR gene and Prostate Cancer:** Since prostate growth is androgen dependent, alteration in the amount or structure of the androgen receptor (AR) may be indicative of tumor progression. AR mutations have been studied in both prostate tumor-cell lines and in prostate cancer in vivo. The first androgen receptor mutation in prostate cancer was detected in a tumor cell line, altering the ligand specificity of the receptor such that estrogens, antiandrogens (and androgens) could act as agonists.\textsuperscript{133,134} The frequency of AR mutations in primary tumors of the prostate is relatively low.\textsuperscript{135} In contrast, a higher frequency of mutations has been reported in bone metastases from patients who did not respond to hormonal therapy. Visakorpi et al. (1995), for example, have shown that up to 30% of prostate cancer specimens from men failing hormonal therapy are characterized by increases in copy number of X chromosomal region (Xq, band 11-13) containing the androgen receptor.\textsuperscript{136}

Another important molecular mechanism which may be involved in failure to androgen deprivation therapy is an amplification of the AR gene.\textsuperscript{136,137} AR gene amplification was observed in 28-30% of recurrent prostate carcinomas from patients treated with monotherapy (orchietomy, n=37; LHRH agonist, n=6; estrogen, n=6; or orchietomy and estrogen, n=5), while untreated primary tumors did not display this amplification. AR amplification was observed in close to 100% of the cells in the recurrent tumors while such a phenomenon was never seen in the tens of thousands of cells screened from many different untreated tumors. Only one mutation, which did not change the transactivational properties of the AR, was found among the 13 AR-amplified cases studied, thus indicating that the AR was functional in these cancers. It is also important to note that AR amplification was associated with a markedly increased level of mRNA expression of this gene. Furthermore, AR amplification was most likely to occur in tumors that initially responded well to partial androgen blockade therapy and whose response duration was more than 12 months. The above authors concluded that recurrent hormone-refractory tumors may not always be androgen-independent, as often thought. Failure to respond to monotherapy may be caused by a clonal expansion of hypersensitive cells that are able to grow despite the residual low levels of circulating androgens. These androgens originate from the adrenal precursors and are converted to bioactive dihydrotestosterone (DHT) in the prostate tissue.\textsuperscript{136,137} In support of this hypothesis, the researchers observed one patient whose tumor
recurred with AR amplification and who was subsequently treated with combined therapy; an excellent initial response to maximal androgen blockade.\textsuperscript{137}

These findings are also in perfect agreement with the conclusion from first clinical results obtained fifteen years ago with combination therapy that prostate cancer is more sensitive to androgens than previously expected.\textsuperscript{138,139} The general belief was that the lack of response to orchiectomy or treatment with estrogens in 20-40\% of prostate cancer patients was due to the pre-treatment presence of androgen-resistant tumors. In fact a large proportion of these tumors are androgen hypersensitive, since their growth can be inhibited by further blockade with the addition of a pure antiandrogen after castration.

Ethnic variation in the AR has also been investigated as a possible explanation for ethnic differences in prostate cancer risk. Interest has focused on a variable region of trinucleotide cytosine-adenine-guanine repeats (CAG\textsubscript{n}, n=number of repeats) in exon 1 of the AR gene. A negative relationship has been observed between CAG\textsubscript{n} length and the regulatory activity of the AR gene.\textsuperscript{140, 141} For example, in an analysis of 57 prostate cancer patients and 39 control subjects, Irvine et al. (1995) have shown that shorter alleles (n<22 repeats) are associated with a slight increase in prostate cancer risk.\textsuperscript{141} This inverse relationship between prostate cancer risk and CAG\textsubscript{n} has been described by other groups of investigators.\textsuperscript{142, 143} Among cancer-free individuals, the shorter alleles are more frequently observed among African-American men than among either Caucasian or Asian-American men.\textsuperscript{144} Coupled, these findings suggest a possible link in the AR with ethnic variation.

3.3.7 Summary

**Genetic Aberrations and Breast Cancer:** Hereditary breast cancer has been associated with alterations in the expression of oncogenes and tumor suppressor genes. Over-expression of the oncogene HER2 in breast cancer cells has been correlated with poor prognosis and resistance to hormonal and chemotherapeutic strategies. Expression of the nuclear factor myc has been used as an independent prognostic indicator in breast cancer, over-expression of which correlates with high tumor grade and intermediate risk of relapse. For breast cancer, Bcl-2 has been correlated with ER-positivity and smaller tumor size. Germ-line mutations in the tumor suppressor gene, p53, have been noted in cancer-prone families with Li-Fraumeni syndrome. p53 protein expression may be used as a marker to identify cases of DCIS which are more likely to progress to invasive carcinoma. The ATM gene confers sensitivity to radiation and is a strong candidate for modifying cancer susceptibility.

The majority of hereditary breast cancers can be attributed to germ-line mutations in BRCA1 and BRCA2. BRCA1 mutations have been shown to have greater prevalence in families in which there is presence of both breast and ovarian cancers. BRCA1-associated breast cancers are often of grade III, over-expressing p53, and are ER-negative. In contrast to BRCA1, BRCA2 has been associated with fewer cases of ovarian cancer and several cases of male breast cancer. The
founder mutations 185delAG and 5382insC in BRCA1, and 6174delT in BRCA2 appear in about two-thirds of ovarian cancer and one-third of breast cancer patients of Ashkenazi Jewish decent.

**Genetic Aberrations and Prostate Cancer:** Altered expression of proto-oncogenes and tumor-suppressor genes appear to play a significant role in the development of prostate cancer. Protein expression of the oncogene Bcl-2 and p53 have a role as independent prognostic markers for disease-free survival after radical prostatectomy. p53 may also serve as a radioresistance marker in patients destined not to benefit from treatment with radiotherapy for localized prostate cancer. Predisposing mutations in HPC1 are responsible for only a minority of familial prostate cancer cases; it is likely to be most important in families of African-American origin and in families with at least four cases of the disease. At present, a number of other genes (for example, AR gene mutations) have also been implicated in contributing to prostate carcinogenesis.

### 3.4 Hereditary Linkage of Breast and Prostate Cancer

BRCA1 and BRCA2 gene mutations have been implicated in prostate cancer. Ford et al. (1994), for example, have reported a three-fold increased risk of prostate cancer in male carriers of the BRCA1 gene. An association between breast and prostate cancer has been demonstrated to date using breast cancer probands; however, this association is in doubt when using prostate cancer probands. Furthermore, the risk for malignancies at other sites appears not to be increased even among families with high prostate cancer prevalence. This latter finding means that hereditary prostate cancer appears to be relatively site-specific and does not appear to be part of another hereditary cancer syndrome. In summary, the real link between breast and prostate cancer is in doubt and needs further assessment.
4. CLINICAL RELEVANCE

4.1 Predictive Ability of Current Detection Methods

From the collection of a blood sample to the final reporting of results, currently it can take as short as 4-6 weeks or as long as 3 months to 2 years to complete a genetic analysis, depending on the nature and number of genes to be fully examined. The time required to perform laboratory analysis can be reduced if it is possible to identify tentatively which gene (among more than one candidate gene) is more likely to carry a mutation based on an individual’s family history. For example, a family that displays several cases of ovarian and breast cancer with the absence of male breast cancer, is more likely to contain a mutation in \textit{BRCA1} than \textit{BRCA2}. If there are cases of both male and female cancer with multiple affected members, the \textit{BRCA2} gene may be suspected. Similarly, problems may evolve when a family has a large number of breast cancers and no other types of malignancies, in which case, both \textit{BRCA1} and \textit{BRCA2} may need to be examined.

Unnecessary testing of large genes such as \textit{BRCA1} and \textit{BRCA2} may prove costly in terms of both human and economic resources. Since evidence of recombination between the disease and either \textit{BRCA1} or \textit{BRCA2} haplotypes would assist in ruling out one or both loci, it would be beneficial to perform a quick linkage test to determine which gene is more likely to contain a mutation.\textsuperscript{152} The value of family studies using polymorphisms is further stressed by a study demonstrating that a stop codon mutation in \textit{BRCA2} did not segregate with the disease phenotype,\textsuperscript{153} and of a second report describing an individual with simultaneous \textit{BRCA1} and \textit{BRCA2} mutations.\textsuperscript{106} The ethnic background of the client must also be considered in genetic testing for breast or prostate cancer susceptibility. For example, in the Ashkenazi Jewish population certain mutations have been identified as likely to occur in carriers of \textit{BRCA1} and \textit{BRCA2}, and therefore the analysis can be targeted specifically to those areas of the genes where mutations have been found to occur. However, there is no guarantee that the test can identify a specific mutation in the \textit{BRCA1} and/or \textit{BRCA2} gene(s) even in a family with a significant history of breast cancer.

Predictive genetic testing requires that an individual’s blood be drawn for DNA analysis following informed consent and genetic counseling. It is important that time and care be taken for blood collection to ensure that each sample is appropriately labeled and stored properly for DNA analysis. The blood sample is then centrifuged, cells are spun off, and DNA extractions are made ready for genetic analysis. The complex organization of genetic aberrations (for example, \textit{BRCA1}), lack of clustering, and the genetic heterogeneity of hereditary disease, make rapid screening in a routine diagnostic setting for either breast or prostate cancer technically challenging.\textsuperscript{80}

In Canada, different clinics offer different types of laboratory analysis. DNA or molecular-based testing focuses directly on an individual’s genotype. There are three main types of molecular testing currently available: indirect DNA analysis, direct mutation detection, and RNA-based functional assays. Technically, analysis of protein products and other functional assays are also
considered forms of indirect testing as they do not detect specific disease-associated mutations.\textsuperscript{154}

The kind of test used can affect the individual because tests have varying accuracies, require more or less cooperation of family members, and take more or less time and money. The ideal criteria for DNA-based genetic tests include optimal estimates of test sensitivity and specificity, throughput and speed of testing that fit into clinical laboratory routine, and user-friendliness.\textsuperscript{155}

\textit{Genetic linkage analysis} is an indirect method of tracking the inheritance of a disease and is used when the gene has been localized to a particular chromosomal region, but its precise location and sequence are not known (for example, \textit{HPC1} gene). In genetic linkage analysis, the relevant regions of the tested individual’s two copies of the chromosome can be compared to the same stretches of those chromosomes in a relative affected with the disease. By using genetic markers as indicators, the test can show whether the individual being tested has inherited the same copy of that part of the chromosome. Generally, a systematic genome-wide search is necessary to produce meaningful linkage data by testing for linkage in large, pooled families.

Linkage analysis is currently used for \textit{HPC1} testing for prostate cancer susceptibility. Linkage analysis may also be offered to women with a family history of early-onset breast or ovarian cancer or Li-Fraumeni syndrome. However, linkage analysis requires samples from affected individuals and their relatives, and by its nature, it cannot be fully accurate. Problems inherent in linkage analysis include errors in typing due to nonpaternity, \textit{de novo} alleles, and misclassification of diagnosis of affected individuals who may have sporadic disease. A lod score of $3.0$, based on analysis of at least 10 family members, is suggestive of linkage. This type of genetic test is also dependent on allele frequencies for the gene markers used, which may vary depending on ethnic population, the penetrance of the disorder for the ages of the individuals in the analysis, and prior probability estimates that the cancer in a particular family is caused by a mutation in this gene.

\textit{Direct automated sequencing} is thought to be the most sensitive and specific mutation detection technique available. Currently, full-scale sequencing of large transcripts such as \textit{BRCA1} or \textit{ATM} mutations are labor-intensive, costly, and problematic for large-scale testing. Gel shift assays including \textit{multiplex heteroduplex analysis} (MHX) and \textit{single-strand conformation polymorphism} (SSCP) can reduce the number of samples that are necessary for sequencing, but the sensitivity of these assays is variable. Assays such as the allele specific oligonucleotide hybridization and \textit{protein truncation test} (PTT) are also available but have the limitation of identifying only specific types of mutations.\textsuperscript{156} New computer-based technologies are currently being developed to fully automate complete gene-sequence analysis. These new technologies are expected to significantly improve the efficiency of mutation detection in a cost-effective manner.\textsuperscript{157}

Once the gene(s) is known and sequenced, other methods can be used depending on the types of mutations in particular gene(s). For example, in the case of hereditary breast cancer, approximately 75\% of mutations in \textit{BRCA1} and \textit{BRCA2} genes are currently thought to result in truncation of the protein, resulting in an altered protein that is significantly shorter than the normal protein.\textsuperscript{158, 81} This protein is thought to send a message to cells telling them to stop
multiplying. If the protein is truncated, the message is interrupted and the wrong message is sent to the cells; cells continue to multiply, resulting in a cancerous growth. Relying on this principle and the fact that 61% of the BRCA1 protein is encoded by exon 11, PTT with its ability to screen segments of up to 2,000 bases, offers an alternative to sequencing of the entire gene. To perform the PTT, a section of the suspected gene, BRCA1 or BRCA2, is used to create proteins in a test tube using the coding DNA strand of the gene, in order to compare it to normal protein. The normal and the newly synthesized proteins are then drawn through a porous gel using an electrical charge. The smaller protein will pass through the gel faster indicating that an altered protein is present, and that a mutation may be present in that section of the gene. If a mutation is not found, the process can be repeated for other sections of the gene.

The PTT is significantly faster and less costly than sequencing an entire gene. However, in the case of BRCA1 and BRCA2, this method is capable of identifying only an estimated 70-90% of mutations, therefore, an individual may be at greater risk of hereditary breast cancer even though the test was negative. If mutations are identified, the result is confirmed by a second laboratory before the client is advised. The test may not be fully informative as BRCA1 and BRCA2 mutations are thought to account for only 80-85% of hereditary breast cancer cases, the remaining 15-20% may be attributed to a gene or a combination of genes that have not yet been identified. However, mutations identified by PTT will have an immediate clinical relevance, whereas amino acid substitutions detected by other methods such as SSCP and direct sequencing may have no causal relation to disease outcome. PTT poses a clear advantage over SSCP when screening isolated index cases. A disadvantage of PTT relative to SSCP is the possibility that truncating mutations decrease mRNA (ribonucleic acid) stability and thereby decrease the ability of detection of the mutated allele derived messenger RNA.

Loss of heterozygosity (one allelic copy of a gene), LOH, is a frequent occurrence in hereditary breast and prostate cancer. LOH can be detected by amplifying fragments of human genomic DNA by PCR. In affected individuals, LOH is detected in matching tumor cellular DNA when the signal corresponding to one of the two alleles is greatly reduced or absent. However, this type of analysis is limited to analyzing specific regions of the gene; for example, detecting loss of part of a chromosome arm in a set of tumors and in the availability of samples and accessibility to specific DNA probes.

The fluorescence in situ hybridization (FISH) technique uses DNA probes to detect the qualitative presence of a gene such as the over-expression of the HER2 oncogene. This assay is used as an adjunct to data obtained by evaluation of other accepted prognostic indicators. To complement FISH, microsatellite analysis has been used to further examine the extent and nature of chromosomal changes. MHX is capable of analyzing a quarter of the coding region in one step, and has been shown to detect approximately 50% of all BRCA1 mutations in breast/ovarian cancer families.

Familial cases of breast cancer and at least one verified case of ovarian cancer imply a greater probability of BRCA1 involvement. However, this probability may vary considerably in
populations. For example, a linkage study of 16 Dutch breast/ovarian cancer families suggested a lower proportion being linked to BRCA1. An unknown proportion of the BRCA1 mutations could be chromosomal aberrations (deletions, duplications, inversions), located outside the regions covered by polymerase chain reaction (PCR), or located in regulatory regions, and would therefore escape detection by PTT or SSCP. The importance to perform Southern blot analysis is well illustrated by the recent finding that three large deletions that are not detected by these approaches comprise 36% of all BRCA1 mutations found in Dutch breast-cancer families to date. The detection of a truncated band migrating at a different patient-specific position is a qualitative test sensitive to a level of 10-20% of the normal mRNA. Successful detection of carriers using RNA has been reported for Duchenne’s Muscular Dystrophy and Familial Adenomatous Polyposis.

Simple, rapid and efficient mutation screening techniques will be necessary to reduce diagnostic workload especially if there is an expected demand for predictive genetic testing. Since a great proportion of BRCA1 mutations result in truncation of the protein, PTT is an attractive method to apply early on in the search. In the case of BRCA1, approximately 50 different gene fragments are analyzed by SSCP. Analysis becomes a laborious task if a large number of chromosomes are to be tested. PCR-SSCP-MHX analysis of pooled DNA has been performed for more rapid detection of germline mutations in BRCA1. Using this method, DNA samples are subjected to PCR prior to SSCP increasing throughput of SSCP analysis in a cost-saving manner, without compromising its ability to detect mutations. If confirmed by other studies, PCR-SSCP-MHX analysis may be a cost-effective alternative to conventional methods. A technique known as dideoxy fingerprinting (DDF), which combines a Sanger sequencing reaction with multiple-fragment single-strand conformation analysis (SSCA), has also been used to detect BRCA1 mutations. DDF was more sensitive than SSCA in that DDF detected all BRCA1 sequence variants, while base substitution BRCA1 mutations were missed by SSCA.

The inherent limitations of test results used to predict onset or the development of breast and prostate cancer are further complicated by medical and ethical issues that surround disclosure of genetic information to at-risk relatives. As with most medical conditions, genetic conditions rarely exhibit homogeneity in terms of disease manifestation among affected individuals. Some genetic conditions such as hereditary breast and prostate cancer are attributed to not only one, but several genes, the combination of which have the potential to produce more complex clinical outcomes. Furthermore, although an individual carrier of a mutant gene within a cancer-prone family is at greater risk of developing a malignancy, nutritional, pharmacological, or other interventions may confer protection. Before findings from studies based on cancer-prone families can be extrapolated to the general population, explicit epidemiological studies of gene-cancer relationships need to be conducted.
4.2 Genetic Counseling

With the isolation and identification of two breast cancer genes, \textit{BRCA1} and \textit{BRCA2}, it is now possible to offer genetic testing to women (or men) with a family history of breast cancer to inform them as to whether they are at greater risk of developing the disease than other members of the general population. In families in which prostate cancer is linked to the \textit{HPC1} locus, for example, men can be identified as having that specific risk factor or not. Because the \textit{HPC1} gene is likely to be identified in the near future, men found to be of carrier status can be studied further whereas, as with \textit{BRCA1} and \textit{BRCA2} testing for women at risk for breast cancer, those without a predisposing mutation have their risk reduced to that of the general population.

Genetic counseling is the communication process by which individuals and their family members (clients) are given information about the nature, recurrence risk, burden, risks and benefits of tests and meaning of test results, as well as counseling and support concerning the implications of such genetic information.\textsuperscript{1} As reflected in the above definition, genetic susceptibility tests provide a very specialized type of genetic information as their results have implications for extended families; as such, they differ from other types of medical tests.\textsuperscript{169} Test results for susceptibility to breast and prostate cancers are probabilistic and not a definite indication that at-risk relatives will develop either malignancy by a certain time.\textsuperscript{170} For these and other reasons discussed in this report, it is essential to provide adequate pretest and post-test education and genetic counseling as well as longitudinal follow-up.\textsuperscript{169, 171}

The major reasons cited in the literature for patients and family members in attending genetic counseling for hereditary cancer are to obtain certainty, to take preventive actions, and to estimate the risk to offspring.\textsuperscript{172} Specifically, based on a study of American women who were first-degree relatives of breast cancer patients, the three most commonly cited reasons for wanting genetic testing for \textit{BRCA1} were to learn about the risk to offspring, to increase use of cancer screening, and to take better care of oneself.\textsuperscript{173} There have not been similar surveys to date for prostate cancer given that its molecular genetic study is still in its infancy.

4.2.1 Pretest counseling

Prior to genetic testing for breast and prostate cancer susceptibility, it is most important to document as accurate a family history as possible. This should comprise of the age of cancer onset, the pattern of multiple primary cancers (including bilaterality of paired organs such as in breast cancer), extension of this information through the patient’s second-degree relatives whenever possible, and exposures to carcinogenic agents.\textsuperscript{174, 169} This information is used to create a family tree or pedigree of at least three generations for both paternal and maternal relatives.\textsuperscript{174} By pedigree analysis, the genetic counselor can advise whether the family history is indicative of the presence of an altered gene and explain the benefits, risks, and limitations of predictive genetic testing for the client.\textsuperscript{173} During this process, sufficient information is necessary within a supportive context for informed consent or informed refusal to predictive testing. The need for a truly informed decision by the client is critical in the case of prostate cancer.\textsuperscript{175, 169}
For breast cancer, high risk families are those identified as having breast cancer extending across three generations, with diagnosis prior to age 50. Families in which there are fewer cases of breast cancer, diagnosis after menopause, and no incidence of ovarian cancer, are classified as moderate-risk. Low-risk families are those which display only one family member with breast cancer. For prostate cancer, on the other hand, high-risk families (based on criteria for hereditary prostate cancer) are those identified as having a clustering of three or more affected relatives within a nuclear family [(for example, a father and two sons), two relatives affected at an early age (< 55 years), or the presence of prostate cancer in each of three generations in either the paternal or maternal lineage (for example, grandfather, father, and son)]. A positive family history increases the relative risk of prostate cancer in male first-degree relatives approximately two-fold in general. The significance of developing an accurate family medical history is so important that prior to a physician being accredited as a medical genetics specialist by either the Canadian College of Medical Geneticists (CCMG) or the Royal College of Physicians and Surgeons of Canada, physicians must demonstrate their ability to elicit a comprehensive medical history with the assistance of their client.176

Pretest counseling can often untangle the confusion and misunderstanding that family members may have about genetic risk. For example, is the breast cancer observed in a particular family due to BRCA1, BRCA2, ATM, or another breast cancer susceptibility gene? Once the correct gene has been identified, probability estimates for a particular cancer can be offered. For women in high-risk families carrying BRCA1 mutations, for example, the risk estimates of developing both a first and a recurrent breast cancer (and inversely the chances of never developing the disease) need to be explained. Moreover, the risk of developing ovarian cancer, and possibly an elevated risk of prostate cancer for male mutation-carriers also needs to be explained. The relative risk for prostate cancer is increased by the presence of multiple numbers of affected relatives and age at onset of the disease. It is imperative that the client be informed of these risk estimates given the evidence to date, and that testing positive for a BRCA1, BRCA2, or HPC1 mutation, for example, is by no means synonymous with a diagnosis of breast or prostate cancer, nor does it mean that the disease is inevitable.

Participants have been known to have preconceived notions about their risk for cancer.170 The advantages and disadvantages of knowing this information should be discussed and considered along with an individual’s mental and emotional state. Much fear and anxiety can be alleviated by presenting the information in a manner suitable to the patient’s comprehension and by providing simple explanations to medical and scientific terminology.177 The amount of information provided to the patient is based upon individual need. Some medical organizations suggest that pretest education be provided not only to the individual seeking genetic testing, but also to her or his family. Predictive genetic testing for hereditary breast and prostate cancer poses complex emotional implications on a family as a whole, and upon individual members of the unit. Several studies have emphasized the importance of pretest education and genetic counseling in minimizing harm to persons who proceed with predictive genetic testing.178, 179 These studies reveal that the at-risk individuals, not just their medical providers, believe these are important components. When used to supplement a face-to-face encounter, educational tools
such as CD-ROMS, videotapes, and pamphlets may enhance communication and assist in the decision-making process. It has been shown that the more personalized the discussion that takes place during counseling, the more thorough the client’s understanding of genetic testing becomes, and the more capable the client is at providing a more informed decision regarding testing.

4.2.2 Post-test counseling

In conventional medicine, information regarding test results is often communicated by telephone. However, because of the complexities associated with genetic risk-factor information, the most efficient means of conveying and receiving test results is in person. It is important to allow for privacy and adequate time for processing the information during notification of test results. The session should be dedicated to dealing with genetic, medical, psychologic, social, and economic implications of test results. Testing implications will differ significantly for breast or prostate cancer, from person to person, and between gender lines (for example, BRCA2-associated male breast cancer). Testing implications may also differ depending on the types of gene mutations being tested. Compared to HPC1, germ-line mutations in p53 and Bcl-2 over-expression may predict transition to hormone-refractory prostate disease. Individuals who receive emotional support from their physician have less anxiety and depression, and this support can have a positive effect on disease progression. Anxiety is the most significant factor to influence a patient’s long-term psychological adjustment to a diagnosis of breast cancer. Increased anxiety may hinder women from seeking care and surveillance for the disease. The need for psychosocial support for clients is necessary especially after the release of test results, irrespective of positive or negative status.

In the event of a positive test result, commonly recommended early-detection strategies include CBE and screening by mammography for breast cancer, or DRE and PSA for prostate cancer. A major difficulty faced by patients and physicians is that while genetic testing may identify an individual at greater risk of developing the disease over her or his lifetime, the question remains as to what intervention, if any, may be offered to prevent onset of the disease. For women of BRCA1 or BRCA2 carrier-status, for example, it is suggested that CBE be conducted by a physician biannually instead of annually. Similarly for prostate cancer, HPC1 carrier-status, would require earlier PSA screening. For male BRCA1 mutation carriers on the other hand, given the insufficient data to date, the “jury is out” regarding earlier surveillance for prostate cancer.

Further decisions regarding preventive treatment are generally based on the experiences within the family, whether one is identified with breast or prostate cancer. It takes courage for individuals to seek information, in so doing they must confront their own mortality or remember the loss of their loved ones who had suffered from the disease. By discussing the limitations and potential risks associated with genetic testing for breast or prostate cancer susceptibility, some individuals may be dissuaded from taking part. An estimated possible false-positive rate of 5-14% makes for difficult decision making regarding prophylactic measures such as a mastectomy.
In view of the lack of randomized treatment studies comparing radical prostatectomy or radiotherapy with watchful waiting for prostate cancer, clinical management must be presented to the client with a clear understanding of the morbidity associated with these treatment options. This information must be conveyed to the client when discussing risks, benefits, and limitations of testing during the pretest phase. Without sufficient information regarding the limitations of genetic testing and management (especially for prostate cancer), patients are more likely to be disappointed with the results, possibly rendering them to further adverse psychological consequences of testing. In this regard, the CCMG expects that its graduates be trained in psychological dynamics, stress management, and crisis intervention, in order to provide psychological support personally or by referral. Genetic counseling thus represents a dramatic change from the conventionally perceived physician-patient relationship.\(^{181}\)

The role of the non-directive genetic counselor is to help individuals reach decisions, taking into consideration all of the above relevant factors. Since genetic testing can’t predict when, or if, breast or prostate cancer may occur or provide an effective cure, it is suggested that a primary focus be given to the patient’s emotional and psychological needs.\(^{169}\) Some individuals find the genetic information complex and overwhelming and would like the genetic counselor to advise them as to what to do. Frustration arises when they do not receive a direct answer. If decision making is relinquished to the physician, the client is left to live and cope with the decision that is made. The CCMG recognizes that physicians need to know how to help patients to understand, cope with, and adjust to sensitive genetic information. The College’s professional accreditation standards require an ability to communicate at a level appropriate to the client. In order to ensure that genetic information is effectively communicated to the client, the genetic counselor must be fully aware of any cultural, linguistic or ethnic differences which might impair communication or understanding by the patient. This is especially evident for genetic testing for breast and prostate cancer susceptibility given the prevalence of specific types of mutations across the different racial/ethnic groups.
5. ETHICAL, PSYCHO-SOCIAL IMPLICATIONS

In recent years, the achievements of the Human Genome Project, the advancement of molecular genetics, and the advent of computer storage call to question the confidentiality of medical information. Advances in the field of genetic research have brought forth the need to address the privacy, confidentiality, and property rights related to requesting, obtaining, testing, storing, and disposing of an individual’s genetic material. Concern arises over defining an individual’s right to control access to their genetic material, the privilege to control the information derived therefrom, and to prevent potential abuse of genetic information by third party members.

As with all other medical information, genetic information is obtained with the patient’s consent to providing a blood sample, in addition to other consent provisions. From this blood sample, nucleic acids from nucleated cells are separated and a genetic test is performed to determine the absence or presence of a particular genetic marker, gene, or gene sequence. The genetic information and information derived from biological samples are stored similar to that from a regular medical exam or a biochemical test.

The information derived from genetic testing poses familial implications as samples containing genetic material, unlike most other conventional medical samples, can be stored indefinitely and genetically analyzed at any point in the future. This raises the concern that new genes and genetic techniques may be discovered after the sample is obtained, and obtaining consent from the sample donor may no longer be possible. By providing samples for genetic analysis, an individual runs the risk of losing some or all control over confidential genetic information.

To ensure confidentiality and respect for client autonomy it is necessary to obtain an individual’s informed consent prior to gathering a genetic sample, to establish full disclosure of the tests to be performed and the effect of the results, and to provide the individual with the ability to forego genetic analysis or request that the sample be destroyed.

Access to genetic counseling is crucial for wise dissemination of genetic information. Four principles of good counseling applicable to hereditary disease are privacy and confidentiality, justice, autonomy (respect for persons), and beneficence/non-maleficence. Privacy and confidentiality require that cautionary mechanisms be in place to ensure that results and sensitive information, such as non-paternity, are not disclosed to third parties without the client’s consent, unless harm might result to family members. Marital and sibling relationships may be problematic or otherwise altered if other family members are made aware of test results. Justice requires that persons be eligible for predisposition testing regardless of ethnic background, geographical location or ability to pay, and that no one experience discrimination based upon their test results. Autonomy is the obligation of having respect for an individual’s right to make informed decisions, the right to know, or not to know the results of a genetic test. This refers to the rights of the client considering testing to be fully informed as to the effects and implications that genetic testing may have on their lives and requires the discussion of all possible outcomes, positive and negative, of genetic testing. This is the basis for honoring and ensuring informed consent. Beneficence is the duty to benefit others and to maximize net benefits, while non-
maleficence is the duty to avoid, prevent or minimize harm to others. It is necessary to consider the potential harm and emotional distress after learning about an individual’s risk level or the results of genetic testing.

5.1 Ethical Issues

As the study of the molecular genetics of breast and prostate cancers progresses, a number of ethical issues will be encountered for genetic testing. These will include issues of informed consent, privacy and confidentiality, and the potential for psycho-social harm. Furthermore, due to its potential impact on family relationships, the family issues complicate informed consent as well as privacy and confidentiality.

5.1.1 Informed consent

The doctrine of informed consent is a direct application of the concept of respect for persons. Informed consent to genetic testing for cancer susceptibility must be obtained before genetic tests are conducted. Consent information should in general emphasize the voluntary and optional nature of testing, the limitations of testing as well as the potential benefits including the accuracy of current diagnostic technologies, the fact that test results cannot provide definitive information about whether or when cancer will develop due to incomplete penetrance of particular gene mutation(s), and limitations in conventional options for screening and treatment. This information should be expressed at the level of understanding and language most suitable to the client. Discussion of risks should at least include the potential for anxiety, altered family relationships (including the risks of misidentified paternity), stigmatization, and discrimination. In addition, clients need to be informed about DNA banking issues including uses for purposes beyond the intent of genetic information for disease susceptibility, and of access to and control over this information.

When considering genetic testing for hereditary breast cancer, the identification of BRCA1/2 carrier status would be of benefit in that it may encourage carriers and at-risk family members to adopt increased surveillance strategies, informed reproductive choices, or prophylactic measures. However, the incomplete penetrance of BRCA1 and BRCA2 limits genetic analysis and interpretation of test results. The incomplete efficacy of mammography, CBE, prophylactic surgery, or experimental gene therapy may further limit benefits to those of carrier status. A randomized controlled trial was conducted to evaluate the impact of pretest education and counseling on decision-making for BRCA1 testing in low to moderate-risk women in the United States. The educational approach provided information regarding personal risk factors, inheritance of cancer susceptibility, the benefits, limitations, and risks of BRCA1 testing, and cancer screening and prevention options. The counseling approach included this information plus a personalized discussion of experiences with cancer in the family and covered the potential psychological and social impact of testing. Both educational and counseling approaches led to significant increases in knowledge with respect to a control group. The counseling approach
appeared to be superior in producing significant increases in perceived limitations and risks of \textit{BRCA1} testing and decreases in perceived benefits. However, neither approach produced changes in intention to undergo \textit{BRCA1} testing. Albeit based on findings from a single US trial\textsuperscript{187}, decision making optimally requires both knowledge and reasoned evaluation of the positive and negative consequences of alternate decisions.

Obtaining informed consent to genetic testing for prostate cancer susceptibility is particularly challenging because of the complexity of hereditary disease (genetic heterogeneity, differences in ethnic background, effect of family clusters), the unpredictable natural history of prostate cancer, the absence of data from randomized trials on treatment efficacy, and adverse treatment effects. In their Guidelines on the Early Detection and Screening for Prostate Cancer, the American College of Physicians (1997) lists eight facts that should be given to participants as part of the informed consent process prior to any testing\textsuperscript{188}. These facts include that the benefits of aggressive treatment for prostate cancer have not yet been proven; aggressive therapy is necessary to realize any benefit from the discovery of the tumor; a small but finite risk for early death and a significant risk for chronic illness is associated with these treatments, particularly regarding sexual and urinary function; early detection may save lives; and early detection and treatment may avert future cancer-related illness. Given the rapid pace of genetic studies for prostate cancer, moreover, investigators may find themselves in possession of information they could use clinically but without a developed program for delivering the information to individuals and families who request early results from the researchers. Approaches to the question of disclosing early results will be needed in the form of decision making guidelines and/or creation and use of committees, analogous to the data safety and monitoring committees in clinical trials\textsuperscript{189}.

The impact of the consent process on decision making for genetic testing is not clear to date. Results from a randomized study on the impact of informed consent for conventional (non-genetic) testing options revealed that patients given information about PSA and prostate cancer were significantly less interested in undergoing PSA testing than controls\textsuperscript{190}. Family history and perceived susceptibility to prostate cancer were associated with increased interest, and advancing age with decreased interest in PSA testing\textsuperscript{191, 192}. A Swedish case-series of attitudes regarding possible inheritance of prostate cancer among sons of men with the disease revealed that 90\% of the unaffected sons (N=100) wanted to know whether prostate cancer was inheritable (66 definitely and 24 probably). They were positively inclined to undergo conventional screening (65 definitely and 27 probably) and to undergo genetic testing (50 definitely and 41 probably) provided there had been multiple cases of prostate cancer in their family\textsuperscript{193}. An interest to know whether they could inherit prostate cancer was more frequent among sons with less than 12 years of education, worries about inheritance, younger age, a father treated with curative intent, and with children of their own, especially if sons\textsuperscript{193}. In this study, educational level was negatively correlated with interest in knowing about the possibility of inheritance and in undergoing testing, whereas by analogy, studies on hereditary breast-ovarian cancer have reported a positive correlation between educational level and request for test results\textsuperscript{194, 178}. These contradictory results could be due to cultural differences, differences between men and women, or both.
5.1.2 Privacy and Confidentiality

Patients have the right to control the use of all medical information about themselves, including genetic information. However, due to both the predictive or risk-assessing nature of genetic information and its potential health implications, participants should be informed during pretest counseling that genetic information about their cancer risk may result in information being recorded in their health records and that such documentation would increase the chances of third parties gaining access to test results. The predictive nature of many molecular genetic tests further sets them apart from conventional medicine. Hospital medical records provide a history of what has happened to a patient to date, but they are not particularly predictive. Molecular genetic tests may be extremely predictive of either the individual or the individual’s family. The privacy and confidentiality issues are further complicated by the personal, yet simultaneously familial, nature of genetic information. This non-individualistic nature of genetic information raises conflicts between the duty to maintain confidentiality and the duty to warn other family members who may be at greater risk of developing cancer.

A study of 544 breast cancer families demonstrated that while 76% of blood relatives were aware of their family history, 24% of relatives were unaware of their relative’s diagnosis or family history of breast cancer and notification occurred when medical personnel contacted them. Such disclosure may detrimentally change an individual’s perception of risk, sense of privacy, and psycho-social well-being. Individuals who were notified about their family history through a large follow-up study were more likely than other family members to be more concerned about developing breast cancer. There was no difference between the proportion of males and females who expressed concern about developing cancer. However, it was unclear whether the men who relayed cancer concern were worried about the fate of their own health, or that of female relatives. Many studies demonstrate that female relatives, especially daughters of breast cancer patients, tend to overestimate their risk of developing breast cancer, while other women at high-risk tend to underestimate their risk. Individuals who were aware of their family history expressed greater concern regarding privacy issues than those who were unaware prior to notification.

Ethical issues associated with the disclosure of a family history of cancer are complex because notification may have a negative impact on the individual at high-risk of developing the disease. The response to notification of a family history of cancer in a distant relative may be quite different from that which might occur when a close relative carries a known cancer-predisposing gene. Greater understanding of privacy and psycho-social issues of family members who are informed about their family history of cancer may assist in developing appropriate guidelines for risk notification. In general, the health care professional may have an ethical duty to warn at-risk family members following failed attempts to encourage disclosure by the client. This is particularly relevant if the genetic information reveals that family members are at a substantially higher risk of suffering from a serious and otherwise undetected genetic disorder and if prevention or treatment is available.
For breast cancer, notification would allow at-risk family members to adopt early monitoring, prophylactic treatment, and informed reproductive choices. The possibility must be considered that within a family, knowledge of genetic information may constitute greater harm than non-disclosure, particularly for those family members who may not wish to know. Potential for harm incurred from disclosure may include psychological, social, financial, and discriminatory harm, stigmatization and labeling, and the potential to lose or encounter difficulty in obtaining employment or insurance. Likewise, failure to disclose such genetic information to at-risk individuals may incur harm by limiting opportunities for prevention and treatment, as well as denying one the opportunity of making reproductive choices. In the case where an offspring of a carrier has been adopted, disclosure of family history by a physician would be of benefit to the individual, at which point he or she may adopt increased surveillance strategies and informed reproductive choices. The question of whether an adoptee has the right to know the identity and characteristics of their biological parents remains to be addressed. While the confidentiality of the adoption process might be jeopardized, physicians acting in the best interest of the child may disclose the potential for a genetically based disease.

For prostate cancer, disclosure of genetic information by the health care professional to at-risk family members without the client’s consent would not be permissible at this stage given the genetic heterogeneity of hereditary disease. Moreover, candidate genes to date for hereditary prostate cancer, such as \textit{HPC1}, explain only a small fraction of the overall familial aggregation of the disease.

\section{5.2 Psycho-Social Issues}

Genetic testing for cancer susceptibility may cause significant psycho-social harm given new knowledge of predetermined risk for this disease. Research into the psychological impact of genetic testing in Huntington’s disease, cystic fibrosis, and hereditary breast-ovarian cancer, has shown that an individual’s decision to undergo testing and his or her response upon receiving the results is influenced by many factors. Uptake rates for genetic tests overall are higher when there are effective ways of treating or preventing the disease. For example, the uptake for predictive genetic testing for Huntington’s disease, for which there is no treatment, is about 10\%; while that for breast cancer, for which there is a possibility of prevention and treatment, is about 50\%. Uptake of genetic tests also depends on how a test is offered, whether it is by invitation by letter or in person.

\subsection{5.2.1 Interest and attitudes}
The identification of *BRCA1* as a breast cancer susceptibility gene has spurred much interest by the public. Research suggests that demand for genetic testing for breast cancer susceptibility is quite high, even among those at relatively low risk of carrying a mutation.\textsuperscript{173} Of those contacted by phone survey, 51% of the general public had heard about the discovery of a breast cancer gene and 69% of respondents said they would be interested in testing.\textsuperscript{203} Women describing themselves as comfortable financially, having some college education, and being premenopausal, were more likely to have heard of the gene discovery than those who were not comfortable financially, had a high school education, and were not premenopausal. Caucasian women of less than 60 years of age who believed their family would benefit if they had a mammogram, and that mammograms give them a feeling of control over their health, were more likely to show an interest in genetic testing than women who were 60 or older, African-American or of other ethnic origin, and who did not hold the above beliefs in the health benefits of mammography.

Surveys of individuals from breast-ovarian cancer families showed that 75-79% of subjects indicated they definitely wished to be tested and 16-20% would probably want testing for *BRCA1* mutations.\textsuperscript{194, 92} Females were significantly more likely to definitely want to be tested.\textsuperscript{92} Women were more likely to accept genetic testing for susceptibility for breast cancer if they were having regular breast examinations by a physician, believed that mammography effectively detects early cancer, and believed that early cancer was curable.\textsuperscript{204} The readiness of women to seek genetic testing for hereditary breast cancer may be attributed to their perception that the advantages of testing outweigh the disadvantages.\textsuperscript{205}

If public interest and demand for genetic testing for breast cancer susceptibility are high, given the media exposure, primary care physicians are likely to shoulder the initial burden of discussing testing with patients and family members. The majority of obstetrician-gynecologists surveyed (81% of 105) in Rochester, New York, believed that current *BRCA1* testing can detect a genetic predisposition to breast cancer accurately enough to be clinically useful. They also believed that women with a family history of breast cancer who are not currently having regular mammography would benefit from DNA testing because a positive result may motivate them to adopt greater surveillance.\textsuperscript{206} Educational resources may assist community-based primary care physicians who need information about testing for inherited susceptibility cancers so they can help patients and their families make informed decisions.\textsuperscript{207}

Research has shown that interest in undergoing genetic testing is more strongly related to perceived risk than objective risk.\textsuperscript{201} For example, candidates with a high self-perceived risk of having an altered *BRCA1* gene were more likely to opt for testing, while their estimated true genetic risk did not predict an interest in the test.\textsuperscript{173} Similarly, an Australian study on men’s estimates of prostate cancer risk showed that they could explain anxiety about prostate cancer, in part, by subjects’ overestimation of the actual risks of the disease.\textsuperscript{208} Thirty seven percent of respondents (N=340) thought that at least 1 in 5 men would develop prostate cancer before the age of 75 years, and 11% thought that 1 in 5 men would die of it. This perception can be compared with actual risks based on statistics from the Australian Cancer Society, of 1 in 18 and 1 in 65, respectively.
It is also important to consider gender associated factors. Although the disease states under review appear distinctly divided along sexual lines, cases of male breast cancer remind us that this division is not absolute. Women are more likely than men to undergo genetic testing.\textsuperscript{209-211} This may be due to differences in their knowledge about health threats and differences in the way they cope with adverse information about their health.\textsuperscript{201} Men are more likely than women to engage in minimisation.\textsuperscript{210,212} Males tend to use mental health services and cancer support groups to a far lesser degree than women. Older men, in particular, are reluctant to seek services and are more likely to hold negative views of mental health issues.\textsuperscript{213}

Besides perceived risk and age, ethnic and cultural factors are important determinants of interest in genetic testing for cancer susceptibility given the differences in ethnic variation in candidate gene mutations.\textsuperscript{171} A specific group of the general population, nearly 1\% of Eastern European or Ashkenazi Jews carry a specific gene mutation that may predispose them to breast and ovarian cancer [based on the 1996 Census, 351,705 individuals of Jewish origin resided in Canada (N=28,528,125) (Statistics Canada, 1998, . 90\% of which are of Ashkenazi descent (Canadian Jewish Congress, Nov. 20, 1998))]. Of the 20 published families with the 185delAG mutation in the \textit{BRCA1} gene, it was discovered that all were of Ashkenazi Jewish decent.\textsuperscript{81} This association between a specific mutation and a genetic sub-population has prompted further study of the Jewish population for research into the prevalence of the \textit{BRCA1} mutation. Samples originally collected for Tay Sachs and Cystic Fibrosis screening, therefore, not specifically chosen for a positive history of breast cancer, showed that 1\% of Jewish samples carry this mutation as derived from a common ancestor. This surprisingly high frequency of the 185delAG mutation has the potential to be the most common serious single-gene disease yet identified in any population group.\textsuperscript{81} It is estimated that this rate of alteration is 3- to 6- fold greater than all \textit{BRCA1} alterations combined in the general population. Investigators remain uncertain as to what extent having this mutation increases a woman’s risk of developing breast or ovarian cancer, or to what extent it might increase the risk for colon or prostate cancer in men. Further research is underway to learn how common the 185delAG alteration is, and to see if people with this mutation have more relatives with cancer.

Differences in ethnic variation in candidate gene mutations are also evident in testing for prostate cancer susceptibility given possible prevalence of the \textit{HPC1} locus in families of African origin, allele-specific differences in the androgen receptor, and in the extent of disease at diagnosis and mortality.\textsuperscript{144,214,127} The level of belief in testing efficacy and also receptivity to the advice of health care professionals are factors shown to be positively and independently associated with the intention to undergo prostate cancer testing in African-American men.\textsuperscript{215,216} [As an illustration, based on the 1996 Census, 137,315 individuals of African origin resided in Canada (N=28,528,125), and 305,290 of Caribbean origin (Statistics Canada, 1998)].

These ethnic differences in risk perception bring forth the concept of \textit{genetic myopia}.\textsuperscript{217} Genetic myopia, genetic testing as a “quick fix,” and the genetic subclass emerge as themes from developing genetic technologies in society. Genetic myopia may occur when everything is viewed from the perspective of genetics, resulting in genetic reductionism and genetic
determinism in society. When all health problems and behaviors become attributable to genes, with no focus on other potential factors, genetic reductionism results. Genetic myopia may seriously undermine cancer surveillance and prevention strategies targeted toward the population at large. The genetic “quick fix” theme views genetic testing as an end in itself, rather than a means to obtain the information, and to value its benefits, limitations, and risk to family members. These issues create potential for a genetic subclass.

Genetic accountability and genetic identity are two additional themes that emerge from testing for inherited breast cancer in the Jewish community. Genetic accountability results when women are deemed to be responsible for seeking genetic information. Historically, Jewish women have accepted the responsibility for testing for Tay-Sachs (in orthodox communities, for example, the rabbis keep the genetic registries and so avoid marriages for Tay Sachs). Testing is only performed for recessive disorders that require two carriers in order for there to be a risk to offspring. In light of this, Jewish women may perceive a social obligation to seek information regarding a genetic predisposition to breast cancer, in part for the sake of their children. With knowledge of carrier status in the parent, prenatal testing is relatively easy and quick, thereby allowing for pregnancy termination. This brings forth the question about whether aborting a fetus is ethical, based on an adult-onset disease for which little information exists regarding penetrance and phenotypic effects of different mutations. Furthermore, would only female fetuses be tested and aborted? If a woman decides not to abort, implications arise for the rights of the child. With the moral and ethical issues raised thus far, offering testing for breast and ovarian cancer susceptibility as part of prenatal diagnosis is inappropriate.

Since women may suffer from breast cancer as early as when they are in their twenties, it becomes a positive duty in Jewish law for teenagers of at-risk families to be tested. The objective of testing for 185delAG at an early age is to alert teenagers about whether they carry the mutation, such that they may perform BSE more frequently and at an earlier age that the general population. The duty for at-risk teenagers to undergo testing is derived from the general Jewish obligation to preserve life and health. Traditionally, in Jewish law, adult status is affirmed at the age of twelve-and a half for girls, and thirteen for boys; at which ages they become liable for all of the duties and prohibitions of Jewish law. As an illustration, another concern for Ashkenazi women is the duty to inform prospective spouses of their carrier status. It is suggested that a woman who is aware of a mutation and its strong linkage to breast and ovarian cancer inform a potential mate such that he can make an informed decision about whether or not to marry her, and if so, he is allowed the right to know such that they can make reproductive choices. This is not a male-female issue. The same would hold true for a man bearing this mutation, since he or his children may be at risk, particularly the female children.

5.2.2 Psychological distress

Naturally, participants who find out that they carry a mutation that predisposes them or a possible child to a disease generally tend to be more distressed than those whose test results are negative.
Paradoxically, some with positive test results may find that reducing the uncertainty of their disease risk decreases their anxiety and allows them to plan their lives, while those who test negative may experience survivor guilt. The risks of psychological distress are likely to be greater when testing is offered in clinical settings that do not provide adequate patient education, genetic counseling, informed consent, and follow-up. Careful assessment of test expectations, mood, and social support may reduce the distress associated with genetic testing and counseling throughout the testing process.

A high level of psychological distress is observed in women with enhanced risk of breast cancer. These feelings often affect their willingness and readiness to bank DNA samples for \textit{BRCA1} testing and the clinician’s ability to engage them in preventive measures. It has been shown that individuals from \textit{BRCA1/2}-linked families who decline genetic testing are at risk for depression, and may benefit from education and counseling even if they ultimately opt not to undergo genetic testing. Pretest psychological distress has been detected in clients awaiting DNA testing for heritable late-onset disorders. Subjects who were more distressed reported a greater incidence of disease in close relatives, the disease having a significant impact on their lives, having considerations against predictive testing, and the expectation that being identified as a gene carrier would have adverse effects. Candidates who expected an increase of personal problems displayed higher avoidance than those who could anticipate a more promising life even with carrier status. Despite the psychological implications associated with testing, most subjects said that they definitely wished to undergo \textit{BRCA1} testing.

A study to examine the relationship between psychological distress and the use of \textit{BRCA1} testing by 149 high-risk individuals from hereditary cancer families, showed that 58% of participants requested \textit{BRCA1} test results, while 42% declined to learn of their genetic status. After controlling for demographic factors and risk status, cancer-specific distress was significantly and positively related to \textit{BRCA1} test use, whereas global distress was unrelated to test use. Genetic testing for hereditary breast and prostate cancer brings forth psychological issues for those of carrier and non-carrier status. \textit{BRCA1} and \textit{BRCA2} carriers bear the stigma of having a defective gene. Testing positive can hold potential negative psychological consequences for the patient, as measured for example by the Impact of Event Scale, especially among carriers with no history of cancer. A high level of depression and anxiety can be associated with the knowledge that one is at higher risk for developing breast and ovarian cancer. It has been suggested that 71% of high-risk women report depression and emotional disturbance and 57% have levels of anger and sleep disturbance. Despite uncertainties, it has been shown that cancer-specific distress symptoms motivate individuals toward \textit{BRCA1} test use. Individuals can incur both physical and psychological harm from prophylactic mastectomy or oophorectomy, potential discrimination in employment and insurance, and damage to personal relationships.

A sense of relief balances anger as an emotional response about breast cancer and a perceived loss of femininity in some individuals after undergoing prophylactic surgery. If a woman tests positive, her partner, family or friends may inadvertently treat her differently, leaving her to feel stigmatized and rejected. Husbands may have great difficulty in expressing their true feelings
regarding their partner’s prophylactic surgery, and may benefit from attending counseling with their spouse.\textsuperscript{200} Similarly, there are potentially adverse consequences regarding a negative result. While 80\% of non-carriers display lowered anxiety, some continue to worry or seek prophylactic surgery or hold survivor guilt.\textsuperscript{173} Non-carriers may also succumb to a false sense of reassurance that they will never fall victim to developing breast cancer and adopt less stringent surveillance, when in fact they retain an overall risk of developing the disease equal to that of the general population.

In a study to investigate the possible negative psychological impact in 2,400 men randomly selected for screening for prostate cancer in Sweden,\textsuperscript{226} an invitation to examination (by DRE, TRUS, and PSA) created emotional stress (as measured by serum cortisol analysis). These elevated levels had decreased to normal two weeks after the screening. The highest cortisol levels were found in men who had undergone biopsies immediately before being informed of the results two weeks after screening. Following disclosure of the results, cortisol levels fell, regardless of the results of the biopsy. The results from this study emphasize the need for higher test specificity and minimization of the interval between a test and informing participants of the results.

The primary goal of genetic testing for hereditary breast and prostate cancer is to reduce mortality, morbidity, and minimize psychological distress through the provision of risk information. Unfortunately, many uncertainties remain regarding genetic testing and the effect it has on an individual’s psychological well-being, family function, and preventive behavior. In developing psychological counseling strategies for high-risk individuals, effort needs to be focused on reducing emotional distress, decreasing perceived vulnerability, and improving adherence to surveillance measures.\textsuperscript{199}
6. POLICY IMPLICATIONS

In addition to ethical and psycho-social issues, there are also public policy issues that will become critically urgent by the availability of more convenient, reliable, and powerful genetic tests for cancer susceptibility. The former issues weigh the interests of participants and those of their at-risk family members to that of a clinician-investigator/genetic counselor within the context of genetic testing. Policy issues, on the other hand, involve weighing the interests of participants to that of society or other third-parties outside this context, for example, employers and insurers for whom the genetic information could have relevance.

6.1 Policy Statements and Guidelines

Various organizations in the United States have issued statements about genetic testing for cancer susceptibility. To date, professional organizations in Canada have issued no similar statements. However, the Canadian Genome Analysis and Technology program (CGAT) initiated a genetic research program to examine the social, ethical and legal implications posed by genetic testing.

The 1994 Statement on the Use of DNA Testing for Pre-symptomatic Identification of Cancer Risk prepared by the NACHGR adopts a restrictive position on the question of clinical application. It concludes that “until more information is available to address these critical issues, offering DNA testing or screening for cancer predispositions outside a carefully monitored research environment is premature”. The American Society of Clinical Oncology (ASCO), which represents practicing oncologists, published a statement in 1996 that conflicts with the NACHGR position. While encouraging further research initiatives, ASCO recommends that “genetic testing should be made available to selected patients as part of the preventive oncologic care of families...”. The statement sets forth practice guidelines stating that the indications of testing are (i) a strong family medical history of cancer or onset of disease at an early age, (ii) a test that can be adequately interpreted, and (iii) results that will influence the medical management of the patient or family member.

The ASCO statement introduces a typology of genetic tests for cancer. Group 1 test results demonstrate the presence, or absence, of a genetic mutation and provide unequivocal clinical benefit. Group 2 tests include genetic testing for breast-ovarian cancer, and apply to those conditions where the “medical benefit of the identification of a ‘carrier’ is presumed but not proven.” Group 3 tests are those whose clinical benefit has not been firmly established. The ASCO document goes on to suggest that oncologists should consider offering genetic testing only to the first two test categories, and that testing for Group 3 is considered “research with unknown clinical implications and should not be offered in a clinical setting.” In contrast to the NACHGR position, ASCO suggests that genetic testing for breast-ovarian cancer should no longer be restricted to the research setting and is now appropriate for clinical use.
current stage of molecular genetic study of prostate cancer, genetic testing for prostate cancer susceptibility at present would fall into Group 3 of the ASCO typology.

In Canada, genetic testing is currently only offered as part of a clinical research program designed to explore whether genetic testing should be conducted as part of routine medical care. By conducting research, one can identify levels of risk associated with various mutations, and develop guidelines regarding medical procedures, psychological counseling, and legal procedures that are in the best interest to the client. Model protocols are currently being developed and tested to identify which approach to genetic testing confers the most benefit to the client.\(^{228, 229}\)

Women found to have genetic mutations predisposing them to breast cancer are recommended to begin taking annual mammograms between the ages of 25 and 35, according to a draft report by a US National Institutes of Health task force. The INSERM task force in France also recommended earlier surveillance (age 30 onwards) for mutation carriers.\(^{230}\) However, there does not appear to be any studies regarding the effectiveness of early mammography in mutation carriers.\(^{231}\) The US company Kaiser Permanente is developing evidence-based clinical practice guidelines for testing individuals for mutations in the *BRCA1* gene which is thought to be predictive of a predisposition toward hereditary breast and ovarian breast cancer.\(^{232}\) Included in these guidelines is a confidential *BRCA1* registry to keep track of their company members who undergo *BRCA1* testing or who may decide to undergo future testing. Patient need, such as that for psychological and social support, is also addressed in the guidelines. In the USA, most new genetic tests do not require approval by the Food and Drug Administration (FDA). Although the FDA states that it has the authority to survey genetic testing, they lack resources to do so at present. As an alternative to FDA approval, biotechnology companies are establishing institutional review boards to undertake an overview of clinical protocols.\(^{232}\)

### 6.2 Genetic Discrimination

As genetic testing for cancer susceptibility progresses from the research setting into clinical practice in Canada, another class of public policy issues emerges, issues regarding parties outside the clinical setting who might use the results of such tests. The ability of genetic tests to predict future health risks could be used to deny life insurance or employment opportunities.\(^{233, 171}\) In the United States, at the federal level, the Health Insurance Portability and Accountability Act of 1996 specifically prohibits the use of genetic information to deny group health insurance coverage when workers switch from one job to another.\(^{233}\) Similarly, the Association of British Insurers had adopted a moratorium since early 1997 on asking people to take genetic tests when applying for life insurance\(^{233}\) (The position of British Life Insurers has changed since January, 1998; no questions asked nor access to medical records for life insurance mortgages under pound sterling 100,000). Regarding employment opportunities, American employers can no longer decline to hire someone based on genetic information if the person can perform the essential functions of the job without posing a threat to himself or herself or to others.\(^{233}\) After hiring
workers, employers can exclude from their health-insurance benefits those conditions which genetic testing predicts if there is an actuarial basis for doing so.\textsuperscript{234}

In Canada, unlike the United States’ private health care system, motivation for such testing by insurers and employers may not be that strong given that most basic healthcare costs are covered by the State. However this practice by insurers and employers may become stronger with the growing interest in privatization of health care in Canada.\textsuperscript{235} Most genetic information currently available would be of relatively low actuarial value, and it is unlikely that any particular genetic test for cancer susceptibility would be considered cost-effective enough to use as a routine insurance screen. However, as more people become aware of their genetic risks, commercial insurers will have to decide whether to seek such information from applicants in their underwriting process. This process will become necessary to address increased economic pressure by knowledgeable consumers and competitors who do use such information.\textsuperscript{188} This latter scenario will be especially applicable to genetic testing for breast and prostate cancer susceptibility given their high public profiles.

The insurance industry, understandably, appears uncertain on how or whether or not to use the results of genetic susceptibility tests to determine individual disease risk.\textsuperscript{236} Part of this problem is based on the fact that tests for genetic susceptibilities continue to be questioned by the researchers themselves. For example, a study by Struwing et al., in the May 1997 issue of the New England Journal of Medicine concluded the life-time risk of developing breast cancer among women having one of the three common \textit{BRCA1/2} mutations, but who are not from high-risk families, to be 56%, not 85%, as previously estimated by extrapolation of data from high risk families. Similarly, these investigators estimated that the chance of ovarian cancer was 16%, not 44%, and there is similarly a 16% risk of prostate cancer.\textsuperscript{71} The design of that particular study has sparked criticism among other investigators who were instrumental in the discovery of the genes. It is thought that a larger study to assess cancer association with other mutations is warranted before the relationship between genetics and cancer risk can be better estimated.

Genetic information in the workplace poses societal risks that affect employment possibilities, health insurance and privacy. Following a conditional offer of employment, employers may require a medical examination, with a physical exam and blood tests that may include genetic analysis. They may request general medical release of an individual’s medical records. Although an employer is prohibited from discriminating based on a disability, it is difficult to prove that the employer did not hire or promote based on information derived by genetic analysis. Employment and health insurance are frequently intertwined. Employers offering self-funded plans may alter benefits to reduce or eliminate coverage for specific conditions or procedures. Since many employers directly review health insurance claims, there is an opportunity for loss of medical privacy in the workplace.

Generally, Canadian federal law prohibits medical testing by an employer before offering a candidate a job.\textsuperscript{235} Therefore, not hiring someone based on a genetic test would also likely violate Canadian human rights legislation.\textsuperscript{235} If exceptions were to arise to this prohibition there
would likely be opposition by many in the scientific and business community coupled with almost certain opposition by the Canadian public. The courts would not have a difficult time interpreting existing Canadian law in such a way that any employment decision based on genetic testing would be considered unfair discrimination and a violation of human rights. Studies to date documenting an increased risk for specific cancers, including prostate cancer, among particular groups of workers are difficult to interpret. Whether this increased tendency is the result of specific work-related exposures or of particular factors in lifestyles is unclear. In this regard, the Privacy Commission of Canada has stated that no surveillance technology is more threatening to privacy than that designed to unlock the information contained in human genes. The Commissioner’s report also emphasizes that people must have meaningful control over the communication of genetic information in the private sector and in governments.

6.3 Genetic Literacy and Legislative Awareness

Control of access to medical information is critical to the autonomy (respect for human dignity) of the individual and their family. However, the ability of outsiders or those without training in genetics to gain access to purportedly confidential medical information suggests a need for greater awareness of the laws governing confidentiality among health care professionals.

6.4 Genetic Services Laboratory

Predictive genetic testing usually requires the drawing of a blood sample from the individual and possibly other family members following their informed consent and appropriate counseling. Samples must be obtained with care to ensure that each sample is appropriately labeled and stored properly for later DNA analysis. DNA samples that deteriorate, are contaminated or mishandled during collection, storage, or testing, can result in false-positive or false-negative results.

In Canada, due to limited laboratory resources, different clinics offer different types of laboratory analysis. In order to shorten the time of testing, PTT is sometimes adopted as a technique of choice. While this process is much faster than sequencing an entire gene, it has some drawbacks. Not all mutations that might be present will be identified. For example, in the case of BRCA1, PTT may identify only an estimated 70-90% of mutations.

Although accreditation programs are being established to ensure a high level of standards for equipment and training of personnel, even the best of laboratories can make mistakes. While the risk of error in predictive testing is considered small, warning clients of the possibility of laboratory mix-ups or sample errors is necessary. Canadian courts have held the hospital that refers samples for tests be obliged to: be aware of the facilities, equipment, resources and laboratory personnel, ensure that it is supervised by a director certified by the CCMG; advise the client of the possibility for laboratory error and of any previous errors; ensure that laboratory
personnel are professionally competent; and advise the client of the average rate for false positive and false negative test results.\textsuperscript{176}

While predictive genetic testing for hereditary breast and prostate cancer is still in the research phase with respect to the discovery of new mutations, early indications suggest that approximately 60\% of women offered a \textit{BRCA1} test for breast cancer susceptibility will take the option of genetic testing. If techniques such as PTT identify most gene mutations, there will need to be a large increase in the number of genetic counselors and clinicians to handle the increased work-load.\textsuperscript{240}

### 6.5 Cost-utility Data and Normative Evaluations

One must also consider the cost of and who pays for genetic testing for hereditary cancer. Thus far, genetic testing is still in the clinical research phase, however cost-utility analysis compared with conventional (non-genetic) testing such as mammography and PSA is needed prior to wide scale implementation. Economic analyses of genetic versus conventional testing options for retinoblastoma\textsuperscript{241} and colon cancer,\textsuperscript{242, 243} for example, indicate that each disease gene must be individually evaluated in terms of current technology, clinical care, and treatment outcomes. When considering the cost of genetic testing for hereditary breast and prostate cancer, factors such as: accuracy of the test; probability of a positive test; cost of testing and counseling; emotional effect of a positive or negative test result; and the effect of a positive or negative test result on compliance with conventional options must be taken into consideration.\textsuperscript{244} Further information regarding population prevalence and penetrance of breast and prostate cancer susceptibility genes is necessary prior to decision making regarding payment for genetic testing.\textsuperscript{245}

### 6.6 Payment for Genetic Testing and Preventive Services: Lessons From Breast Cancer

Currently in Canada, predictive genetic testing for \textit{BRCA1} has remained within the domain of the cancer geneticist. Although at an early stage of development, genetic testing is fast becoming an option on a private commercial basis. Due to the ethical and psychological issues associated with genetic testing, the availability of wide-scale commercial testing poses considerable controversy.

While the US-based company Genetics and IVF Institute of Fairfax, Virginia, had begun to offer screening for a \textit{BRCA1} mutation, researchers suggest that testing for the mutation be confined within the realm of the research setting until true risks associated with the mutation are determined.\textsuperscript{232} In late 1996, the US company Myriad Genetics, in Salt Lake City, Utah, began to offer wide-scale genetic testing for mutations in the \textit{BRCA1} gene. Myriad Genetic Laboratories now offer three testing options for analysis of both \textit{BRCA1} and \textit{BRCA2} genes.\textsuperscript{246} The type of test
is the same as that conducted in Canada; however, turn around time is shortened because of computerized auto-sequencing equipment. Myriad doesn’t exclude from testing those without a history of breast cancer. The test involves attending a local Canadian cancer genetics clinic, where a small sample of blood is drawn and sent to a laboratory in the USA. The sample is analyzed and a report of the client’s test result is sent in confidence to the referring physician to ensure that the client receives adequate genetic counseling and understands the test results. Test results are provided to the client accompanied by post-test education and counseling as needed. Follow-up may also include an individualized risk management plan offering testing to blood relatives when appropriate.

The US company OncorMed Inc. of Gaithersburg, Maryland, has received the first FDA approval to market the gene-based test for assessing the risk of developing lymph-node negative, invasive breast cancer. OncorMed’s gene detection system is a FISH (DNA probe) assay that determines the qualitative presence of the \textit{HER2} gene in formalin-fixed, paraffin-embedded human breast tissue. It is indicated as an adjunct to existing clinical and pathologic information currently used for the prognosis of localized breast carcinomas. The US pharmaceutical company Genentech Inc., has developed a new drug, Herceptin, that targets the \textit{HER2} gene. Genetic testing for this gene is offered by OncorMed. Herceptin was approved for the treatment of metastatic breast cancer on September 28, 1998, by the US FDA.

Although commercial developments are progressing to offer genetic testing for hereditary breast cancer, there is controversy about its usefulness for the general population. While mutations in \textit{BRCA1} and \textit{BRCA2} may account for the majority of hereditary breast cancers, overall, these genes account for less than 10% of all breast cancers. A negative result in a mutation test holds no guarantee that the disease will not manifest by other means. Similarly, those who test positive for carrier status may never progress to develop breast cancer.

Additional issues to be considered with respect to testing are cost and responsibility for payment. The approximate cost for such a test runs in the order of US $1,500 per test. Some insurance companies may compensate for such tests, and subsequently raise the premiums of those who receive positive test results. In order to avoid such an ordeal, and in the absence of adequate privacy protection, many clients may prefer to pay for the tests themselves and avoid the risk of increased premiums or canceled policies in the event that their results be disclosed to their insurance company. Standard insurance application forms provide full access to all medical records. Women who test positive for an altered gene may be denied health insurance even though breast cancer has not developed.

Although predictive testing is attractive in that it offers the prospect of early intervention for hereditary breast cancer detection and treatment, and may reduce the risk of disease occurrence, Canadian ministries of health must consider the costs of its implementation. Critical issues of concern include: the cost of wide-scale screening when the incidence of occurrence is low; the sensitivity, accuracy and quality control of genetic testing; whether or not there is adequate means of intervention to halt disease progression upon implementation of testing; and
identification of who, when, and for what reasons individuals should be offered genetic testing. In order for governments to aptly fund genetic testing for breast cancer, they must be able clearly to measure and define its benefits. For example, the genetic testing may enable early detection and encourage participation in surveillance programs resulting in medical efficiency. This novel, “preventive medical care” approach, emphasizing surveillance to maximize prevention, early detection, and survival, could reduce health care costs related to treatment.
7. **CONCLUSIONS**

1. Breast and prostate cancer are the second leading causes of death and the most frequently diagnosed malignancies in Canadian women and men, respectively. Age, ethnicity, and family history are definite risk factors for breast and prostate cancer.

2. Hereditary breast and prostate cancer have been associated with alterations in the expression of tumor suppressor genes and oncogenes.

3. The majority of hereditary breast cancers can be attributed to germline mutations in $BRCA1$ and $BRCA2$, with the remaining cases attributed to over-expression of oncogenes and other genetic aberrations. $BRCA1$ mutations have been shown to have greater prevalence in families in which there is presence of both breast and ovarian cancers. $BRCA1$-associated breast cancers are often of grade III, over-expressing $p53$, and are ER-negative. In contrast to $BRCA1$, $BRCA2$ has been associated with fewer incident cases of ovarian cancer and several cases of male breast cancer. The founder mutations 185delAG and 5382insC in $BRCA1$, and 6174delT in $BRCA2$, appear in about one-third of breast cancer patients of Ashkenazi Jewish decent.

4. Protein expression of $Bcl-2$ and $p53$ genes have roles as independent prognostic markers for disease-free survival after radical treatment. Predisposing mutations in $HPC1$ are responsible for only a minority of familial prostate cancer cases and they are likely to be most important in families of African-American origin and in families with at least four cases of the disease. The identification of prostate cancer families should lead to the identification of further genetic susceptibility genes, although by analogy with $HPC1$, the process is unlikely to be simple. Nevertheless, this might produce an exploitable tumor marker, however the problem of what action to take with the individual would still have to be faced given the limitations in conventional treatment options. Current conventional markers such as PSA are organ-associated rather than tumor-associated, which the ideal marker should be. Consequently, the likelihood of false-positive or negative results is high. The characteristics of an ideal marker(s) should include detection of the presence of a tumor, its malignant potential, its stage in the progression pathway, and the extent of spread.

5. Key ethical implications arising from genetic testing for hereditary breast and prostate cancer include: informed consent, privacy and confidentiality, and familial implications. Significant psychological factors including stigmatization, lowered self-esteem, and anxiety are experienced by those of both carrier and non-carrier status. Predictive genetic testing for breast and prostate cancer has brought forth social issues such as the potential creation of a genetic subclass. Ethnic and gender issues compound the risk of genetic discrimination faced by carriers seeking insurance, employment, or adoption.
6. Currently, genetic testing in Canada is only offered as part of clinical research programs that explore genetic testing as a potential component of routine medical care. As public awareness and new technology develops, the pressure for greater genetic testing services is inevitable. Given the high public profile, vested private sector interest due to potential financial gain, and ethical, psycho-social, and policy implications associated with testing, it would be of benefit to establish clinical research guidelines for predictive genetic testing for families with significant family histories. For both breast and prostate cancer susceptibility, these guidelines would include: (i) a process for ensuring up-to-date information of the medical issues such as a standing panel comprising relevant disciplines (molecular genetics, gynecology/urology, and oncology); (ii) detailed training for health care professionals who provide information and counseling in this area, including CCMG certification in molecular genetics for the laboratory director, or the American equivalent; (iii) the placement of genetic testing services in appropriate centres (for example, CCMG accreditation for laboratory testing); (iv) non-directive counseling (pre- and post-test, and follow-up) on the ethical, psycho-social, and policy issues; (v) the importance of obtaining informed consent; and (vi) encouraging individuals to participate in research.

7. Further studies including extensive research involving larger subsets of families will be required to further identify and assess genetic determinants of breast and prostate cancer. These studies should focus on positive predictive value, accuracy, reliability, sensitivity, and cost-utility of genetic testing compared with conventional testing options.

8. Hereditary disease accounts for a low proportion of the total number of breast and prostate cancer cases. The adoption of each of the above components of clinical research guidelines would require major planning and resources; however, the considerable economic and societal burden of these malignancies and their treatments, coupled with the projected large increase in the number of new cases, makes this a sound investment for Canadians.
8. FUTURE PROSPECTS

Gene therapy is a therapeutic approach that attempts to attack a tumor by using the appropriate oncogene or tumor suppressor gene therapy for cancer. There are three methods of gene transfer: the first is to administer the gene to the patient by injection into muscle or thyroid tissue; the second uses a viral vector to transfer the gene; and the third uses liposomes to package DNA. DNA-mediated gene transfer commonly results in only transient effects of the gene in the target tissue, whereas most viral-mediated gene transfers can lead to permanent gene integration. Retroviruses and adenoviruses are most commonly used. With the former, it is easier to make replication-defective retroviral vectors which integrate the gene permanently into target cells and only into actively dividing cells.

Adenoviruses infect most cell types, have a high efficiency of transfer, and do not require cell division. Liposomes are positively charged lipid membranes that complex with DNA. Since mutations in the BRCA1 gene have been noted in cases of hereditary breast and ovarian cancer, a phase I trial was conducted to explore the possibility of BRCA1 gene-replacement as a potential gene therapy for ovarian cancer. The trial demonstrated that BRCA1 could be transferred to ovarian cancer cells using a retroviral vector with minimal risk of peritonitis or tolerance. The highest human dose level used four daily injections totaling $4 \times 10^{10}$ vector particles each month for two to four months. Eight of 12 patients showed stable disease for 4-16 weeks, and three showed tumor reduction. Parenteral gene therapy using p53 has been shown to inhibit human breast tumors by an antiangiogenesis mechanism without evidence of toxicity.

Just as it is possible to replace gene function using gene therapy, it is possible to inhibit gene function using “antisense.” Antisense-oligonucleotides are chemically modified stretches of single-stranded DNA that are complementary to mRNA regions of a target gene and are capable of specific gene inhibition. Recently, Bcl-2 antisense oligonucleotides have been shown to improve the chemosensitivity of human melanoma grown in mice, suggesting that by reducing Bcl-2 in melanoma one can improve chemosensitivity and treatment outcome. A phase II study of weekly intravenous antibody to HER2 was also shown to inhibit the growth of breast cancer in patients exhibiting HER2 over-expression. Greater understanding of the molecular basis of hereditary breast cancer brings forth new opportunities for more target-specific, effective treatment strategies.

If the absence of p53, HPC1, or another tumor suppressor gene proves to be a significant contributor to prostate carcinogenesis, what if it were possible to “turn on” normal p53 (or HPC1) function? Likewise, if over-expression of Bcl-2 or another oncogene is confirmed to enhance prostate carcinogenesis, what if it were possible to “turn down” Bcl-2 expression? As understanding of the molecular biology of prostate cancer grows, the number of molecular targets for prostate cancer gene therapy has also increased. Different forms of gene therapy are already being investigated and several (Phase I) clinical trials are underway. The therapeutic genes being evaluated by these and other forthcoming trials include antioncogenes (for example, as
with the case of breast cancer, antisense blockade of Bcl-2 expression) and tumor suppressor genes (for example, adenovirus-mediated \textit{p53} gene therapy)\textsuperscript{258, 259}.

These new approaches may lead to treatments for breast and prostate cancer that are less toxic and more effective than current methods for controlling these diseases. With this new technology also come new ethical responsibilities (due to psycho-social and policy issues) to ensure that these strategies are safe for both patients and health care professionals.
9. METHODOLOGY

Published literature was obtained using a number of bibliographic databases. The databases and the search strategies are listed in Table 1. Searches were limited to English language articles and to human studies.

Review literature was identified by searching MEDLINE for 1997. Comprehensive searches of the electronic databases MEDLINE, CancerLit, EMBASE and HealthSTAR from 1990 to 1997; BIOETHICSline, PsycINFO, Social SciSearch, and Sociological Abstracts from 1994 to June, 1998, were conducted using molecular genetic keywords (Table 1). Hand-searching of journals, bibliographies, and database searches of Current Contents (Clinical Medicine Abstracts) were performed to keep abreast of new developments (Table 1). A selected number of reference textbooks were purchased at the inception of the report based either on book reviews in peer-reviewed journals or in consultation with experts in the field.

Relevant articles were retrieved, reviewed and classified by subject. Two members of the project team independently reviewed the above database searches to identify relevant articles for this report. Review articles were the primary reference source for Appendices 1 and 2 (Background and Significance) of the report. Secondary references for these Appendices sections were identified (and retrieved) based on citation in relevant review articles. The latter references were selected to provide an overview of specific areas (for example, range of data estimates), and were usually pooled analyses (for example, meta-analyses, economic analyses) cited in multiple review articles. Relevant Canadian citations (task reports from 1990 onwards, studies published in Canadian peer-reviewed journals) were actively searched for and retrieved, where applicable.

A network of individuals from across Canada from relevant disciplines provided scientific and content advice. Additional literature was retrieved based on subsequent suggestions by the reviewers of this report.
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* or ?? or ?= truncated term
APPENDIX 1

1. Breast Cancer

1.1 Burden of disease

Breast cancer is the second leading cause of death due to cancer in Canadian women and the most common cancer to affect women. Each year in Canada, an estimated 19,300 women are diagnosed with breast cancer and 5,300 women die of this malignancy. A significant proportion are lost during their child-bearing and economically productive years. Twenty-two percent of breast cancer cases occur in women under age 50, 44% occur in women aged 50 to 69, and 34% in women aged 70 and over. Overall, 1 in 9 women is expected to develop breast cancer during her lifetime, and 1 in 25 women is expected to die of breast cancer. Over the past decade, the recorded breast cancer incidence has risen steadily due in part to the implementation of mammographic examinations.

Family history is a significant risk factor contributing to the development of breast cancer. In comparison to environmental factors, genetic factors confer greater increased risk of breast cancer for women whose first-degree relatives (mother, sister, or daughter) are affected by the disease. Risk of breast cancer is influenced by age, hormonal and dietary factors. The potential years of life lost as a result of breast cancer is 97,000 years, as compared to 25,000 years for ovarian cancer and 35,000 years for prostate cancer, reflecting the relatively young age at which women die of breast cancer. Although breast cancer is a disease which primarily affects women, approximately 1% (1,600 of 180,000 new cases of breast cancer) were diagnosed in men, and roughly 400 men died of the disease in the United States in 1998. Given the tremendous impact that breast cancer has on society at large, the 1st World Conference on Breast Cancer was held in Kingston, Ontario, in July of 1997 in order to gain worldwide perspectives on breast cancer.

1.2 Clinical presentation

Breast cancer most commonly affects cells of the milk ducts, and is therefore called “ductal carcinoma.” Approximately 5-10% of cancer originates in the lobules and is termed “lobular carcinoma.” Cancer of the latter type typically affects both breasts. Breast cancer is generally classified as invasive or non-invasive. Invasive cancer originates in the lobules and/or milk ducts, while non-invasive or in situ cancers are confined to the lining of the lobules or ducts. The most common type of non-invasive cancer is “ductal carcinoma in situ” (DCIS). If given sufficient time, DCIS can develop into invasive cancer thus warranting their removal. “Lobular carcinoma in situ,” on the other hand, is considered an early-warning sign for future potential cancerous growth, and surveillance is recommended.
Cancerous cells confined to the milk ducts, and/or gland, are considered “primary cancer.” Over time these cells can proliferate and invade other body parts via lymph nodes or the bloodstream leading to “invasive cancer.” Thus, the most important criteria for assessing future risk of invasive disease is to determine whether cancer cells have invaded the lymph nodes.\(^{268}\)

Breast cancer is commonly categorized into three grades according to growth rate. Features of the tumor such as tubule formation, mitotic count and nuclear size are used for assessment and define histological grade. Well-differentiated tumors are termed as grade I; moderately differentiated tumors as grade II; and poorly differentiated tumors are termed as grade III.\(^{269,267}\) Some cancers grow slowly and are rarely fatal, whereas others start slowly but progress faster and become more aggressive. The third grade type is the most aggressive in growth and results in the lowest chance of survival. Current conventional detection methods cannot easily differentiate between the various grade types.

There are three common causes of benign breast lumps: fibroadenomas, gross cysts, and fibroglandular changes.\(^{261}\) Fibroadenomas are round, circumscribed, firm, moveable, and feel similar to cysts. In contrast to cysts which tend to develop later in life, fibroadenomas tend to occur in younger women. Fibroglandular changes are usually painful and symmetric; they occur most often in the uppermost outer quadrants of the breast and lack clear demarcation.\(^{261}\)

1.3 Conventional screening options

Breast cancer surveillance comprises of three standard methods: clinical breast examination (CBE), breast self-examination (BSE), and mammography.\(^{264}\)

**Clinical Effects:** The Canadian National Breast Screening Study (NBSS) demonstrated the usefulness of frequent CBE in the diagnosis of early-stage, node-negative disease.\(^{270}\) Using CBE, lump detection of less than 1 cm may be difficult;\(^{271}\) it is therefore important that the person who performs the exam be knowledgeable and experienced. Health care professionals who perform CBEs on a regular basis have the best track record for discovering breast lumps. A proper, thorough examination should be conducted noting any recent differences between breasts in size, shape, skin texture, color, nipple discharge or inversion.\(^{261}\) During the NBSS, data collected prospectively suggested that performance of systematic BSE including the components of visual examination, the use of the middle three finger pads, and a well-defined search pattern and search area, may reduce the risk of death from breast cancer. In order for BSE to be effective, it must be implemented when the tumor is detectable and curable. BSE was found to be most effective when performed two years prior to the diagnosis of breast cancer.\(^{272}\) A monthly BSE should be performed one week after the onset of menstruation. In so doing, it is possible to detect either pain or a hard lump in the breast, upper clavicle area, or armpit; spontaneous nipple discharge or scaling; or any swelling, redness or skin irregularities.\(^{265,261}\) The greatest reduction in mortality due to breast cancer occurs when diagnosis is made prior to the cancer developing to form a lump or mass.
Studies suggest that screening mammography significantly reduces breast cancer mortality in women. However, due to breast density, it is often difficult to read mammograms of women under the age of 30, thereby resulting in little benefit. Optimal mammographic imaging is normally conducted using two views of each breast with spot compression and/or magnification views of abnormal areas. Two-view mammography detects more cancers, reduces recall rates, and is more cost effective than single-view mammography. An experienced radiologist may be able to clarify the nature of a mass. Irregular or clustered calcifications within the mass increase suspicion of a carcinoma. However, the overall sensitivity of mammography in palpable breast cancers is thought to be no greater than 82%, and may be substantially lower in pre-menopausal women. Health care professionals must consider both the individual’s risk status and the results of a CBE in order to determine whether it would be considerably difficult to interpret the results of a mammogram. If the breasts are too lumpy, ultrasound may be recommended to distinguish solid from liquid lumps, the latter of which are rarely associated with cancer. Anywhere from 30-60% of positive mammogram results are false positive. Frequently, a second test is required not because of a suspected positive, but due to difficulty in reading the mammogram X-ray. American studies, for example, indicate that up to one-third of the mammograms were of poor quality and required repeat testing. Hormonal therapy and high-fat diets can cause some breasts to become dense, making mammogram X-ray reading difficult to interpret. In order to alleviate unnecessary additional anxiety, it is important to convey that an additional mammogram may not be required as a result of a potential diagnosis of breast cancer, but that it may be due to the individual’s breast type, the time of month, diet, or a poor-quality X-ray. Whenever there is doubt in the interpretation of a mammographic image, the opinion of a second radiologist should be sought for confirmation.

Screening mammograms are those performed when mammography is carried out in the absence of abnormal symptoms for the purpose of early cancer detection. If a screening mammogram indicates an abnormality, further high-quality mammograms are conducted to define the extent and location of the abnormality. Magnification and spot compression views administering local pressure, are used to displace surrounding breast tissue to clarify small densities.

When cytologic examination, mammography, and physical examination all indicate cancerous growth, a biopsy is conducted. A small piece of breast tissue is removed and examined under a microscope noting any irregularities. Core biopsies, clinically or image-guided, can be used to establish or exclude malignancy, thus reducing the need for a surgical biopsy. The procedure involves obtaining 1 to 6 slender cores of tissue for histological diagnosis, to differentiate invasive disease from non-invasive disease, and determining hormone receptor levels. The aim of surgical biopsy, or lumpectomy, is to remove the whole lump in one piece along with a surrounding cuff of normal tissue for evaluation by a pathologist.

**Economic Effects:** A cost-effectiveness analysis based solely upon different mammographic screening strategies demonstrated that the most cost-effective screening strategy is biennial mammography for women aged 50 to 79 years at marginal cost per year of life saved of US $16,000. Based on American estimates, adding annual mammography for women of 40-49
years of age increases the marginal cost per year of life saved to US $20,000 but is more cost-effective than other tested protocols.\textsuperscript{275} Subsequent cost-effectiveness analysis of breast cancer screening was recently conducted in Catalonia, Spain.\textsuperscript{276} During this study, a breast cancer screening program was implemented to screen 100,000 women of 50-64 years of age. The probability estimates used in this study were (i) participation rate of 70%; (ii) sensitivity of 92%; (iii) specificity of 94%; and (iv) 0.36 detected breast cancers per 100 women screened. The estimated total cost was US $2.1 million, with US $1.4 million for mammography and CBE, and US $0.7 million for the detection of the true positive mammographic results by medical re-examination and biopsy. The cost per woman screened was US $30, with an estimated 252 cases of breast cancer detected using this program. The cost-effectiveness ratio obtained from the study was US $8,424 per cancer detected. Cost-effectiveness in terms of cost per life year gained obtained in other studies has ranged from US $3,400 to US $50,000.\textsuperscript{277} Assuming an average increase in life expectancy of 3.2 years in women screened in Spain, for example, the cost-effectiveness ratio in terms of cost per life year gained would be US $7,020.\textsuperscript{276} Cost estimates for a national mammography screening program have also conducted in Australia.\textsuperscript{278}

A recent screening study was conducted by the Conseil d’évaluation des technologies de la santé du Québec (1993).\textsuperscript{279} It suggests that a program using a 12-month screening interval, resulting in a 10\% reduction in breast cancer mortality rates, would prevent 39 breast cancer deaths per year at a cost of CAN $634,000 per death prevented, or CAN $26,700 per year of life gained. If such a program were to reduce mortality by 20\%, 78 breast cancer deaths would be prevented and the cost-effectiveness, not accounting for discounting, would be approximately CAN $13,300 per life-year gained.

\textbf{Recommendations from Professional Groups:} In general, an annual CBE is recommended beginning at age 40; as well as a monthly BSE; and a single baseline mammography at age 35-39, then every 1-2 years for those aged 40-49, and annually for those 50 years of age and older.\textsuperscript{280, 264, 265} At present, there exists considerable debate as to whether mammograms should be offered to all women of ages 40 to 49. In January 1997, the “consensus conference” of the American National Institutes of Health (NIH panel) reported insufficient evidence to support routine mammograms for all women aged 40-49. Supporters of mammographic screening argued that the NIH panel had misinterpreted the scientific evidence, and that early detection is the most effective strategy against breast cancer. In late March, the American National Cancer Institute refused to follow the NIH panel’s report, and advocated that mammogram screening be conducted for women aged 40-49. Critics of mammography for women under the age of 50 are of the view that it offers relatively few benefits, saving the life of only 1 in 1,000 women, and increases exposure to radiation.

At present, Canadian clinics report significant differences in the timing and frequency by which they conduct mammogram surveillance, flagging the need to establish guidelines that are appropriate for high-risk women. Sensitivity of annual mammography plus clinical examination, using the ratio of cases detected by screening to all cases, was 88\% in women aged 50-59 and
81% in women aged 40-49. Specificity, using a surgical biopsy as the definition of a positive case, ranged from 96.5% to 99.9%.\textsuperscript{264}

1.4 Conventional treatment options

Once the nature and extent of the tumor have been established by clinical and mammographic examination, a diagnosis of a clinical stage I or II breast cancer forms the basis for a treatment strategy comprising breast conserving surgery (BCS) followed by radiotherapy.\textsuperscript{261}

**Clinical Effects:** Randomized control trials demonstrate that the outcome of patients with operable breast cancer after BCS with radiotherapy was equivalent to that of a radical mastectomy with respect to distant recurrences and overall survival.\textsuperscript{281, 282, 261} In 1990, the US National Cancer Institute Consensus Conference endorsed BCS as appropriate and desirable treatment for early-stage breast cancer.\textsuperscript{283} The advantage to BCS, also referred to as lumpectomy or wide local excision, is that the tumor is removed along with a cuff of normal tissue, while preserving the cosmetic appearance of the breast.\textsuperscript{284} In contrast, a mastectomy refers to removal of the entire breast, including the nipple and areola complex and the fascia over the pectoralis muscle while sparing the underlying muscles and innervation. Neither BCS nor mastectomy includes removal of the axillary lymph nodes, but lymph node dissection is ritualistically carried out when treating invasive disease.\textsuperscript{261} A disadvantage of BCS is that it must be combined with radiotherapy to ensure its effectiveness.\textsuperscript{285}

The most frequent radiotherapy schedule used in Canada is 50 Gy in 25 fractions to the whole breast without a boost when the excision margins are clear of the disease. Alternative schedules that may be implemented range from 40 Gy in 16 fractions to the whole breast, with or without a boost, to 45 Gy in 25 fractions with a boost of 16 Gy in 8 fractions to the primary site. Irradiation of the whole breast rather than part of the breast is recommended.\textsuperscript{261}

In addition to being time-consuming, radiotherapy may be logistically difficult and costly for patients who live long distances from treatment centres. Radiotherapy may also be accompanied by adverse effects such as swelling, pain, skin pigmentation and fibrosis of the breast. Risk of recurrence is reduced with increasing use of chemotherapy. Local recurrence drops from 13% to 2.5% with the use of sequential methotrexate and 5-fluorouracil, and 0.6% with the use of cyclophosphamide-methotrexate-fluorouracil therapy.\textsuperscript{281}

For women with estrogen receptor (ER)-positive tumors, tamoxifen produced equivalent changes in recurrence rates. It has been suggested that patients who are at risk for systemic metastases be given a 12-week course of chemotherapy followed by radiation therapy, rather than radiation therapy followed by chemotherapy.\textsuperscript{286, 287} Breast cancer recurrence necessitates a second, wider excision or mastectomy. The initial choice between BCS and mastectomy for stage I and II tumors depends upon individual circumstance and personal preference, with the aim of reducing psychological distress and trauma. However, if (i) the risk of local recurrence is visible on a mammogram; or (ii) physical disabilities preclude the use of radiotherapy; or (iii) the tumor is
large in proportion to the breast size; or (iv) the patient’s psychological state warrants, then a mastectomy should be considered. A mastectomy is usually required when a mammogram shows widespread clusters of malignant-type calcifications throughout the breast, when there are multiple tumors, or when there is a lack of definition of the margins of the tumor.

**Economic Effects:** The total cost of medical care for the treatment of patients with breast cancer over a 4-year period correlates with the clinical stage at the time of the initial diagnosis. Higher total costs were incurred for patients with advanced disease at diagnosis (clinical stage III and IV) as compared with patients of stage 0 to II at diagnosis. The cost for all stages of disease has been found to diminish after 1 to 2 years, with the exception of stage II, which increases slightly in years 3 to 4. For example, the cost-effectiveness of routine postoperative radiotherapy after BCS has been calculated in a prospective randomized trial in the United Kingdom comparing sector resection plus axillary dissection for stage I breast cancer. Taking into consideration the cost of primary treatment, follow-up, treatment of local recurrence, travel expense and indirect costs, the estimate of cost per avoided local recurrence at 5 years was £27,018 sterling. Adjustment for quality of life showed a cost of approximately £128,000 sterling per quality adjusted life year gained. The cost of routine postoperative radiotherapy after BCS and axillary dissection for stage I breast cancer per avoided local recurrence and quality adjusted life year gained is high, and shows variation dependant upon the assigned utility value.

**Recommendations from Professional Groups:** For patients with a stage I or II breast cancer, BCS followed by radiotherapy is generally recommended. The US National Institutes of Health Consensus Conference states that lumpectomy is the preferred treatment when compared to a mastectomy because it provides equivalent survival and preserves the breast. In the absence of sufficient reason for selecting mastectomies, the choice between BCS and mastectomy may be made according to the patient’s circumstances and personal preference. Removal and pathological examination of the axillary lymph nodes should be standard procedure for patients with early, invasive breast cancer. Women at high risk are advised to undergo adjuvant systemic therapy. Chemotherapy is recommended for all pre-menopausal women of less than 50 years of age and for postmenopausal women 50 years of age and older with ER-negative tumors. Tamoxifen daily for 5 years, is recommended as the first choice for postmenopausal women with ER-positive tumors, with additional benefit being offered as adjuvant chemotherapy. Two optimal adjuvant chemotherapy regimens are recommended by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer (1998): (i) 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil; (ii) 4 cycles of adriamycin and cyclophosphamide.
APPENDIX 2

2. Prostate Cancer

2.1 Burden of disease

Prostate cancer is the second leading cause of male cancer deaths after lung cancer. It is the most frequently diagnosed malignancy in Canadian men, with an estimated 4,300 deaths and 16,100 newly diagnosed cases in Canada in 1998. Furthermore, 1 in 8 Canadian men will develop prostate cancer during their lifetime while 1 in 26 will die of it. Age, ethnicity, and family history have been firmly established as risk factors for prostate cancer. Other multiple risk factors have been thought to play a role in the epidemiology of prostate cancer, including dietary influences, environmental toxins, and hormone levels. According to projections made prior to the availability of testing in Canada for prostate specific antigen (PSA) levels, the incidence of prostate cancer was forecast to increase to 26,900 cases by the year 2010 and to 35,200 cases by the year 2016. This steadily increasing number of new prostate cancer cases have serious implications for our health care system. Based on 1986 estimates, the economic burden of illness, disability and premature death caused by cancer in general exceeds $9 billion per year in Canada. More than $7 billion of this amount is due to the indirect costs of premature mortality. Given that prostate cancer is responsible for 35,000 years of potential life lost (in 1995), representing 3.9% of the premature mortality caused by cancer, this translates to an estimated $270 million (1986 dollars) of lost productivity as well as the direct economic and human costs. The 1st National Prostate Cancer Forum was held in Toronto, Ontario, on February 27 to March 2, 1997 to develop a consensus to prioritize the actions needed to improve the prevention and early detection of prostate cancer, as well as for improvements in treatment and care.

2.2 Clinical presentation

Prostate cancer is a complex disease, both biologically and clinically. The clinical presentation of prostate cancer varies from small incidental carcinoma to aggressive metastatic disease. That is, it ranges from an indolent form that may never cause clinical symptoms to an aggressive form that is commonly fatal. The long potential latent stage gives rise to the oft-heard quote that “more men die with it than from it.” Histological examination is the only way to definitively diagnose prostate cancer. The most commonly used histological grading system is the Gleason score, which assigns a grade of 1 (most differentiated pattern) to 5 (least differentiated pattern) for each of two predominant patterns of the pathologic specimen, yielding a Gleason sum of 2 to 10. For prognostic purposes, as with breast cancer, the histological results are usually categorized into three grades: low grade 2-4, medium grade 5-7, and high grade 8-10. Once a diagnosis has been established, treatment often depends on clinical and pathologic staging. The two predominant clinical staging systems presently used for prostate cancer are the Whitmore-Jewett (ranging from A to D) and the TNM (tumor, node, metastasis) systems.
2.3 Conventional screening options

Conventional screening methods for prostate cancer are digital rectal examination (DRE) and measurement of PSA. These tests are useful in deciding whether a transrectal ultrasound-guided (TRUS) biopsy of the prostate is indicated or not.

Clinical Effects: The DRE has been the physician’s primary screening tool during routine health examinations. However, its true sensitivity and specificity remain unknown due to a lack of both uniformly performed biopsies and long-term follow-up of the screened population in published studies.\(^\text{188}\) The inability of DRE to detect tumors in the anterior and medial lobes of the prostate (leaving up to 40% of tumors beyond reach), and inter-examiner variability, limit its relative sensitivity as a screening test for prostate cancer.\(^\text{264, 293, 294}\) Representative estimates of positive predictive value and overall cancer detection rate among men 50 years of age or older, range between 15% to 30%, and 1% to 2% respectively.\(^\text{293, 294}\) The positive predictive value of DRE varies relatively little with age.\(^\text{294}\) Abnormal results on DRE increase the odds of a clinically significant intracapsular prostate tumor (>0.5 ml) 1.5 to 2 fold and increase the odds of extracapsular disease 3 to 9 fold.

Measurement of serum PSA is currently the most sensitive non-invasive screening test for prostate cancer. Compared to DRE, the principal advantage of PSA is its ability to detect prostate cancer at an earlier stage.\(^\text{264}\) In addition to the earlier discovery of cancer, PSA also provides detection of indolent cancer (length time bias).\(^\text{295}\) Most of the evaluation of PSA has focused on its positive predictive value, due to substantial uncertainty about the ability of PSA measurement to predict clinically significant prostate tumors given that elevated PSA levels have been observed in men with benign prostatic disease.\(^\text{264, 293, 294}\)

PSA levels greater than 4.0 ng/ml are often considered suspicious in the most commonly used immunoassays; although this threshold is somewhat arbitrary, given the evidence that PSA levels are age-dependent.\(^\text{293, 294}\) For PSA levels between 4 and 10 ng/ml the positive predictive value is about 20%. This value increases to between 42% and 64% if the level is greater than 10 ng/ml.\(^\text{294}\) Use of PSA measurement alone results in cancer detection rates of 2% to 4%.\(^\text{293, 294}\) As with DRE, positive predictive value appears to vary little with age, which suggests that increased disease prevalence is balanced by decreased test specificity in older men.\(^\text{294}\) Elevations in PSA levels between 4 and 10 ng/ml increase the odds of clinically significant intracapsular tumors 1.5- to 3-fold and the odds of extracapsular tumors 3- to 5-fold.

Given the available evidence, the odds both of clinically significant prostate cancer and of detecting early-stage disease are generally higher with PSA measurement as compared to DRE.\(^\text{293, 294}\) Current conventional markers such as PSA are organ-associated rather than tumor-associated, which the ideal marker should be. Consequently, the likelihood of false-positive or negative results is high. The ideal marker(s) should detect the presence of a tumor, its malignant potential, its stage in the progression pathway, the extent of spread, and as an added bonus, be organ-specific.\(^\text{296}\)
Economic Effects: In a recent cost-effectiveness analysis that accompanies the American College of Physicians guidelines on screening for prostate cancer, Coley et al. (1997) estimated that, under a favorable set of assumptions for screening and treatment, one-time testing with DRE and PSA measurement increases average life-expectancy by approximately two weeks. This increase is at a cost per year of life saved of US $12,491 at 50 to 59 years of age, US $18,769 at 60 to 69 years of age, and US $65,909 at 70 to 79 years of age. These estimates are more favorable than the results obtained from an earlier decision analysis by Krahn et al. (1994) in terms of increase in average life expectancy (1 to 2 days) for men aged 50 to 70 years and cost-effectiveness (US $127,000 per life-year saved, without quality adjustments). When quality of life estimates were included in the latter analysis, both DRE and PSA measurement were dominated (greater cost and less health benefit) by no screening.

From the perspective of Quebec’s public health care system, the cost-effectiveness ratio of PSA screening and treatment with radical prostatectomy for localized prostate cancer has been estimated at CAN $214,000 per life-year saved (under conservative estimates with health benefits discounted at 5% over 15 yrs). Data from the above economic analyses are difficult to interpret given their different model structures, context, and timing.

Recommendations from Professional Groups: Given its low positive predictive value to date, and the unknown efficacy of current treatment options, the Canadian Task Force on the Periodic Health Examination (1994) declined to recommend PSA screening for prostate cancer for men over 50 years of age. It concluded that there was insufficient evidence to recommend for or against the use of DRE in the periodic health exam. Systematic reviews by the British Columbia (B.C.) Office of Health Technology Assessment (1993) and the Conseil d’évaluation des technologies de la santé du Québec (1995) recommend against the use of PSA as a routine screening test. The American College of Physicians (1997), and the US Preventive Services Task Force (1996) also do not recommend routine use of PSA.

Conversely, the Canadian Urological Association, the American Urological Association, and the American Cancer Society recommend annual screening for men beginning at 50 years with both DRE and PSA, with consideration of earlier screening for men in high-risk groups, including those with a strong family history of prostate cancer. In addition, The American College of Physicians (1997) encourages physicians to enroll eligible men in ongoing clinical studies when feasible. Prospective randomized trials such as those of the US National Cancer Institute (prostate, lung, colon, ovary) and the European Cancer Program (European Randomized Study of Screening for Prostate Cancer) are underway. Results are expected by the year 2007, showing, it is hoped, a 20% reduction in the death rate in the screened population with DRE and PSA measurement. In this regard, forthcoming results from an analysis of the 1988 Quebec prospective randomized control trial on prostate cancer screening has demonstrated a 69% decrease in the incidence of deaths due to prostate cancer in the screened (DRE and PSA at first visit followed by PSA alone at follow-up visits) compared to the unscreened populations.
2.4 Conventional treatment options

Treatment choice for prostate cancer depends primarily on the stage of disease at diagnosis. The histological grade, patient’s age, and general health are also considered. For men with cancer apparently confined within the prostatic capsule showing no clinical evidence of nodal involvement or metastases, the alternative treatment options are (i) expectant management (“watchful waiting”), delaying radical or systemic treatment until the cancer shows sign of progression, (ii) radical prostatectomy and (iii) radical radiotherapy. The latter two options aim to eradicate the disease.\textsuperscript{293, 297, 306}

Clinical Effects: Most of the data on watchful waiting are based on observational studies conducted in Scandinavian countries, where prostate cancer has traditionally been treated conservatively. Chodak et al. (1994) conducted a meta-analysis of six studies on this subject, providing individual data on 828 patients with a mean age of 70 years followed for an average of 80 months. At the time of the analysis, 72 men had died of prostate cancer and 243 from other causes.\textsuperscript{307} Disease-specific survival in 757 men whose tumors were low or medium grade was 87\% at 10 years compared with 34\% among the 62 men with high grade tumors. Similarly, metastasis-free survival at 10 years was related to histological grade: 81\%, 58\%, and 26\%, for low, medium, and high grade tumors, respectively. In the absence of randomized studies and further longer-term data, watchful waiting appears to be an appropriate treatment choice for older men whose life expectancy is less than 10 years and who have low to medium-grade cancers.\textsuperscript{293, 306} Patient preferences need to be taken into account when considering watchful waiting for the above indications given, for example, the psychological distress resulting from living with a potentially fatal disease.

Improvements in surgical techniques (nerve-sparing prostatectomy) and increased understanding of prostate anatomy have made radical prostatectomy a safe treatment option for localized prostate cancer.\textsuperscript{293, 306} The benefit that can be attributed to radical prostatectomy, however, remains uncertain due to a lack of well-designed controlled studies to date.\textsuperscript{297} For example, a multi-centre pooled analysis of 2,975 radical prostatectomies performed on men with clinically localized disease, reports 5-year metastasis-free survival ranging from 88\% to 100\% for low grade tumors, from 88\% to 92\% for medium grade tumors and from 56\% to 91\% for high-grade tumors.\textsuperscript{308} The complications of radical prostatectomy include operative mortality, incontinence and impotence. The rates of complication vary between studies because of differences in route of access (perineal as opposed to retropubic), patient characteristics, and variable periods of follow-up. Reported mortality rates for radical prostatectomy range from 0.3\% to 2\%; incontinence rates, 1\% to 27\%; and impotence rates, 20\% to 85\%.\textsuperscript{309}

Radiotherapy is a treatment of choice for patients with localized disease who are less fit or who have shorter life-expectancy (<10 years) than those referred for radical prostatectomy.\textsuperscript{293, 306} It is not certain, however, that radiotherapy has the same cure rate as radical prostatectomy because of too few direct comparisons (randomized controlled trials) to date. A number of uncontrolled retrospective series reviewed by Adolfsson (1995), have reported on disease-specific survival
following radiotherapy, which range from 74% to 96% at 5 years and from 62% to 86% at 10 years. Radiotherapy is also not without side-effects and risks. Potential complications of radiotherapy include death (0.2% to 0.5%), incontinence (1% to 3%), impotence (40% to 67%), and acute gastrointestinal or genitourinary complications (3% to 67%). These estimates vary because of differences in radiation dose, mode of technique (conformal as opposed to conventional therapy), and patient characteristics between studies. Current developments in radiotherapy which are still investigational include brachytherapy, using seeds containing iridium-192 and palladium-103, or iridium wires. Early results with brachytherapy are encouraging for treatment of localized disease in appropriate patients.

Hormonal (anti-androgen) therapy is often the first line of treatment for lymph-node or disseminated metastases either on initial diagnosis or when presented as a relapse from failed local therapy (when a patient exhibits symptoms). Additionally, anti-androgen therapy can be used either as a palliative measure, or in an adjuvant or neoadjuvant fashion with radical prostatectomy or radiotherapy for clinically localized disease. Bilateral orchiectomy (surgical castration) and analogues of luteinizing-hormone-releasing-hormone (LHRH) (medical castration) are commonly used for these indications. Eliminating or minimizing the supply of androgenic hormones (testosterone, dihydro-testosterone) usually slows the disease progression since up to 80% of prostate cancers require these androgens for growth. Both treatment modalities have been shown to have an equivalent effect in randomized trials in disease-free intervals. However, the former offers immediate relief from metastatic pain and eliminates problems of compliance with drug treatment, while the latter, given the reversal of side effects by drug withdrawal, may be more psychologically acceptable to many patients.

Orchiectomy and LHRH analogues have an effect on testicular androgens; neither can block the effect of active androgens formed locally in the prostate from inactive adrenal steroids. Indeed, the human adrenals do not secrete testosterone and the most active dihydrotosterone (DHT). The adrenals instead secrete large amounts of the inactive precursors dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S). These inactive-precursor steroids are released into the circulation and then reach the prostate as well as a series of other peripheral tissues where they are converted intracellularly into testosterone and DHT. In men the amount of testosterone and dihydrotestosterone made locally in the prostate from DHEA and DHEA-S is approximately equal to the amount of testosterone and DHT.

The action of adrenal androgens can be stopped by addition of androgen receptor antagonists (for example, flutamide) to surgical or medical castration to give “a maximum androgen blockade” (MAB). A recent meta-analysis of nine randomized trials supports a beneficial effect on survival for MAB using nonsteroidal antiandrogens (flutamide and nilutamide) compared with castration alone. Eventually, unless the patient dies of another condition, virtually all advanced prostate cancers will escape from control of anti-androgen therapy (for example, hormone-refractory disease), and will require other treatments such as chemotherapy or localized radiotherapy.
**Economic Effects:** In general, cost estimates for radiotherapy are lower than those for radical prostatectomy or for palliative measures for advanced disease. No precise economic comparisons between treatment modalities are possible to date in the absence of data from well-designed randomized prospective trials, and given differences in published analyses regarding cost measurement (exclusion from consideration of direct personal and indirect treatment costs, i.e., out-of-pocket costs to patients such as urinary pads required for incontinence and lost productivity, respectively). Given this state of uncertainty about the relative merits of the current treatment options, several investigators have published decision models of treatment for localized prostate cancer. For example, Fleming et al. (1993) concluded that under the most optimistic estimates of treatment efficacy, radical prostatectomy or radiotherapy increases quality-adjusted survival by less than one year in patients aged 60 to 65 years with high grade tumors. This effect is observed when compared to a strategy of watchful waiting; under lower estimates of treatment efficacy, watchful waiting was always equal to or better than radical prostatectomy or radiotherapy. This decision analysis has, however, been criticized regarding the accuracy of its probability estimates and discounting used for complications. Four randomized trials (one in the USA, one in the United Kingdom, and two in Scandinavia) addressing the question of radical versus conservative management for localized prostate cancer are in progress which will include measurements of quality of life and economic costs, but it will be many years before their results will be available.

**Recommendations from Professional Groups:** In a report prepared for the health technology assessment panel of the National Health Service for the United Kingdom (NHS panel), Chamberlain et al. (1997) concluded that the effectiveness of the three methods of management for localized prostate cancer is not known because of a lack of direct comparison to date between these therapeutic options. However, given its lower incidence of side-effects, the NHS panel recommends watchful waiting as a treatment of choice for men with less than 10 years of life expectancy and for those with clinically localized, low grade disease. The review by the American Urological Association Guidelines Panel for the Management of Clinically Localized Prostate Cancer also makes it clear that the outcomes of these treatment methods could not be compared because of extreme variation in the patient populations that had been assigned to these therapeutic options. For treatment of advanced disease, the NHS panel recommends that, until further data from current research trials are available, treatment by maximum androgen blockade should only be undertaken in the context of a randomized controlled trial.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
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<td>androgen receptor</td>
<td>16*</td>
</tr>
<tr>
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</tr>
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</tr>
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</tr>
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</tr>
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</tr>
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<td>57</td>
</tr>
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</tr>
<tr>
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</tr>
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<td>56</td>
</tr>
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</table>

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REFERENCES


119. Schubert EL, Lee MK, Mefford HC, et al. BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. *American Journal of Human Genetics* 1997;60(5):1031-1040.


Harris SE, Rong Z, Harris MA, Lubahn DD. Androgen receptor in human prostate adenocarcinoma LNCaP/ADEP cells contains a mutation which alters the specificity of the steroid-dependent transcriptional activation region. *Endocrinology* 1990;126:93.


76


221. Peters JA, Stopher JE. Role of the genetic counselor in familial cancer. Oncology (Huntington) 1996;10(2):159-166, 175.


244. Singer ME, Cebul RD. BRCA1: to test or not to test, that is the question. Health Matrix 1997;7(1):163-185.


