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**AN INVESTIGATION INTO THE RISING INCIDENCE OF
CARCINOMA OF THE PROSTATE IN CANADA**


by

ISRA GABRIEL LEVY

A thesis submitted to the
School of Graduate Studies and Research
in partial fulfilment of the requirements for the
M.Sc. degree in Epidemiology

University of Ottawa

August 1993

 **Isra Gabriel Levy, Ottawa, Canada, 1993**



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"What a man doesn't understand, he doesn't have..."
Johann Goethe (1749-1832)

"The improvement of the understanding is for two ends: first, for our own increase of knowledge; secondly, to enable us to deliver, and make out that knowledge to others..."
John Locke (1632-1704)

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SUMMARY

Objectives

The purpose of this study was to analyze prostate cancer trends in Canada, determine whether the observed trends are associated with earlier detection, assess the association between prostatectomy rates and prostate cancer incidence rates and assess other possible reasons to explain the observed trends.

Methods

Mortality, incidence and surgical procedure data were derived from Statistics Canada databases, and age-standardised rates calculated. Linear regression of national and provincial prostatectomy rates on prostate cancer incidence rates was performed. A chart review was undertaken at the Ottawa Civic Hospital. Charts of a random sample of incident cases diagnosed during two time periods (1976 and 1986/1987), and a random sample of pathology records of men whose prostatectomy samples were diagnosed as benign during the same times, were reviewed.

Outcome Variables

Age-standardised rates of mortality and incidence from prostate cancer were calculated, as were rates of prostatectomies, and linear correlations between them. For chart reviews changes were assessed between 1976 and 1986/7 in: 1) stage

distribution of cancer cases, 2) distribution of cases detected incidentally following surgery for suspected benign prostatic hypertrophy, and 3) the average number of slides analyzed per 10 grams of tissue submitted from prostatectomies.

Results

Canadian age-adjusted incidence rates increased by 71% between 1969 and 1988, and mortality rates increased by 23%. Rates of prostatectomies increased by 55% between 1970 and 1987. There were significant positive linear correlations between the Canadian ($r=0.94$) incidence and prostatectomy rates over time, and between rates for each of the provinces during a three year period ($r=0.72$).

Results from the chart review revealed that during 1976 53% of the cancers diagnosed were localised (stages A or B), while during 1986/7 75% were localised ($p=0.01$). Extrapolation of these proportions to the general population suggests that most of the increase in the observed incidence rates can be attributed to an increase in rates of localised disease. The proportion of cancers diagnosed incidentally among men undergoing transurethral prostatectomy increased by 11%, although the numbers of procedures did not increase in the hospital. Significantly ($p<0.001$) more slides were analyzed by pathology staff for every 10 grams of curettings submitted in 1986 versus 1976.

Conclusions

Correlations between prostate cancer incidence rates and prostatectomy rates suggest that increased surgical treatment of benign prostatic disease contributed to the increase in incidence rates through increased detection of latent cancers. This hypothesis is supported by the chart review, which is the first work to show an association, other than an ecological one, between TURPs and the increased detection of prostate cancer. The increase in early stage cancers, especially incidentally discovered cancers, and the discovery of increased scrutiny of surgical specimens by histopathological staff, corroborates the ecological data. Although elevations in unestablished risk factors may have contributed to the observed increase in incidence, much of the increase can be attributed to an increase in rates of localised disease. This suggests that the increases may be due to early detection and not risk elevation.

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INTRODUCTION

The Significance of Prostate Cancer in Canada

Prostate cancer is the second commonest non-cutaneous malignant neoplasm occurring in Canadian men. In Canada it is currently estimated to be responsible for 20% of new cancers and 12% of cancer deaths among males, second only to lung cancer¹. It is the commonest site of new cancers in men aged 75 years and over². Figure 1 shows the breakdown of cancer incidence in males, over the period of 1984-1988².

Over the last two decades reported incidence and mortality rates due to prostate cancer have steadily increased³, and in parts of western Canada the number of new cases is now estimated to exceed that of lung cancer¹. It has been projected that by 1995 this situation will exist in Canada's most populous province, Ontario⁴. The Canadian rate is already among the three highest international rates⁵, and the lifetime probability of a Canadian male developing prostate cancer is now 8.75%¹. In 1992 an estimated 12,000 new cases, and 3,700 deaths, were attributable to this disease in Canadian males, accounting for 27,000 potential years of life lost (compared to age-specific life expectancy)¹.

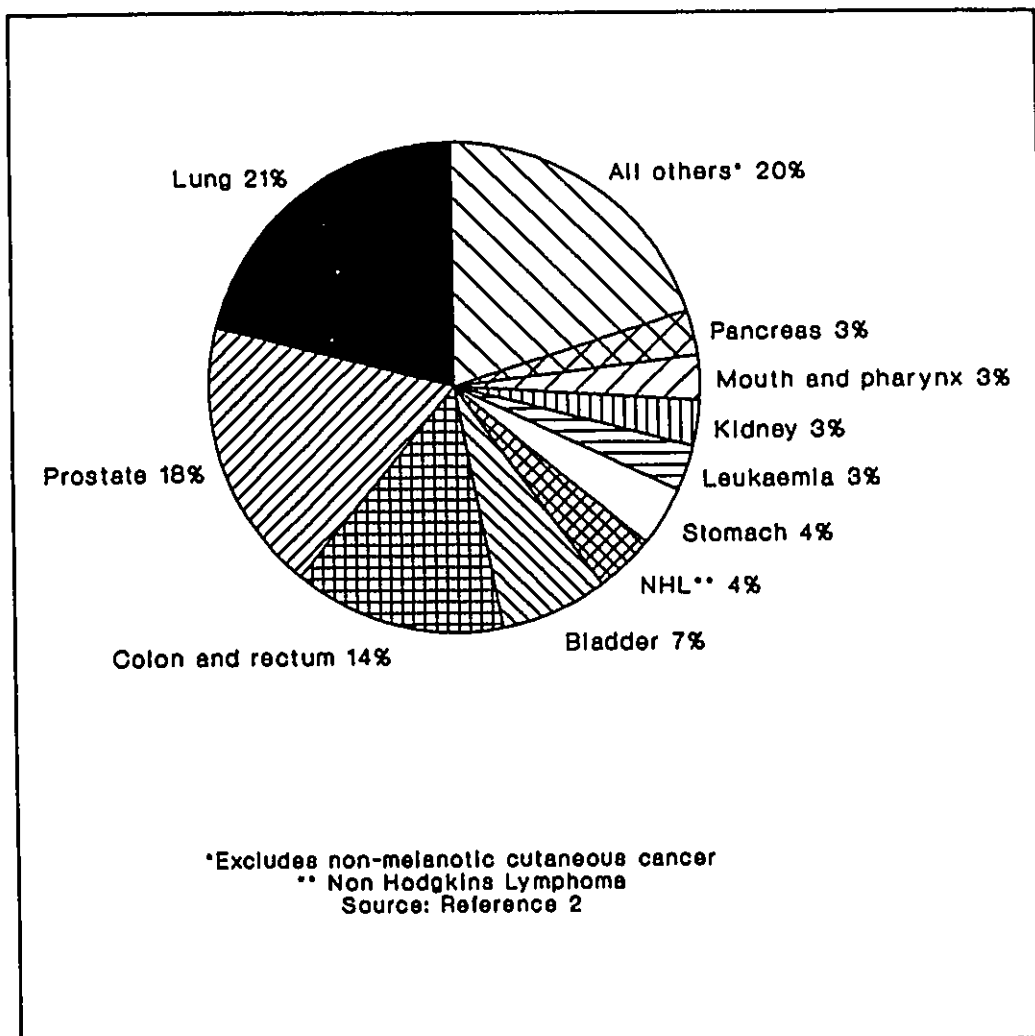


FIGURE 1 The distribution of the 10 most common cancers in Canadian males, excluding non-melanotic cutaneous cancers (1984-1988)

Epidemiological Background

The causes of prostate cancer remain unknown. There is substantial variation in occurrence around the world, with rates in North America and Northern Europe being relatively high compared to those in Southern Europe, and considerably higher than those in Asia⁶⁻⁸. There is also a racial difference in incidence rates, with the disease being commoner in blacks than in whites in areas of high incidence.

The range of occurrence of the disease is, therefore, very wide, from an age-standardised rate of 0.8/100,000 in Chinese to one of 100.2/100,000 in black Californians⁹. Rising rates are found among various groups migrating from low to high risk geographical areas¹⁰⁻¹². These observations, and others showing the presence of birth cohort effects in various populations¹³, suggest an aetiological role for modifiable environmental factors. Several factors have been proposed as possible risk factors. Dietary fat and vitamin A¹⁴⁻¹⁶, and cadmium exposure through cigarette smoke or occupation¹⁷ have been associated with the development of the disease. Studies examining the relationship of prostate cancer with sexual habits, sexually transmitted diseases, and androgenic sex hormone levels have also been performed⁹, and recently much debate has centred around the role of vasectomy as a risk factor¹⁸⁻²¹. Other reports have linked the occupation of farming to the disease^{22,23}, possibly related to exposure to pesticides²³. However, epidemiological studies have failed to determine, conclusively, a causal agent^{9,19,24}, and only increasing age and a positive family history^{9,25-28} can be considered as definite risk factors.

The information presented above is to enhance the reader's understanding of the subject of prostate cancer. The focus of the study reported in this thesis was to ascertain possible explanations for the rise in incidence observed in Canadian men over recent years. The investigation of aetiological factors was not a feature of this work.

Clinical Features and Natural History of the Disease

Early in the clinical course of prostate cancer there may be no symptoms or signs associated with the disease. As the cancer progresses symptoms of bladder outlet obstruction, or prostatism, may occur. An examining physician may be able to detect changes in the size, shape or consistency of the gland, whether or not symptoms are present, through digital rectal examination (DRE). Later in the course of a clinically aggressive tumour's natural history metastatic disease occurs, and symptoms and signs become manifest in relation to the nature of the metastases, e.g., pain from bone involvement, shortness of breath from lung involvement, etc.

However, prostate cancer varies greatly in malignant aggressiveness. It is accepted that cancers which would not have behaved in an aggressive way, and become clinically manifest, are sometimes detected during the course of other medical interventions^{13,29,30}. These cancers are termed "latent" cancers, as they have not manifested at the time of their discovery. Some latent cancers are probably of the clinically aggressive type, and would likely have progressed and presented with clinical disease if they had not been discovered early. However, a very large proportion of latent cancers never become clinically aggressive³¹⁻³⁶, and the discovery of such tumours does not provide the patient with any benefit consequent on early diagnosis. Furthermore incidence rates include these cancers, and so this phenomenon may distort the epidemiological picture of the disease in an unhelpful way^{13,37}.

Benign prostatic hypertrophy (BPH) is a non-malignant enlargement of the prostate gland which leads to bladder outlet obstruction and symptoms of prostatism. It is often treated by surgical methods, using some or other variety of prostatectomy. BPH is extremely common, and its development increases with advancing age. More than two thirds of men over the age of 50 years have evidence of BPH, and it has been estimated that a 50 year old male has a 20-25% lifetime probability of undergoing a prostatectomy³⁰. The commonest form of prostatectomy performed in North America is the transurethral prostatectomy (TURP)^{30,37,38}, representing more than 95% of prostatectomies performed in certain areas³⁸.

Latent cancers are usually discovered when a man undergoes prostatectomy for bladder outlet obstruction. Chips of prostate tissue are routinely subjected to histological examination to confirm that the surgeon has removed prostate tissue, and to make a pathological diagnosis on the specimen. On occasion the examining pathologist interprets the specimen as containing malignant cells, and thus the diagnosis of a latent cancer is made. This type of cancer is also referred to as "incidentally diagnosed" cancer, or simply "incidental cancer". Latent cancers are known to be prevalent in many populations, and the prevalence increases in men of increasing ages^{31,32,39-44}.

Clinical Presentations

Given the natural history of the disease described above, one of three sets of circumstances usually precedes the diagnosis of prostate cancer:

- i) The patient has no symptoms. Evidence of prostatic cancer is detected by a physician (usually a primary care physician) through a DRE during the course of a routine physical examination or an examination for an unrelated medical problem; the suspected diagnosis is then confirmed by obtaining prostatic tissue for histological examination, usually through a needle biopsy or prostatectomy.

- ii) The patient has symptoms of prostatism but there is no clinical reason leading the primary care or specialist physician to suspect cancer. BPH is diagnosed clinically, and a prostatectomy is performed as a therapeutic manoeuvre. However, malignancy is diagnosed incidentally during routine histological examination of the tissue obtained during prostatectomy. Under these circumstances the prostatectomy can be thought of as a diagnostic procedure, having enabled the diagnosis of prostate cancer to be made.

- iii) The patient has symptoms and signs which suggest to the examining physician that the diagnosis may be that of cancer, e.g., there is a palpable nodule on rectal examination or bony or perineal pain. The diagnosis is confirmed by examining tissue derived from a prostatectomy procedure, or from a needle biopsy.

The issue of mass screening of asymptomatic people for prostate cancer has been the subject of much debate. New technologies, such as the blood test for prostate

specific antigen (PSA) and the transrectal ultrasound (TRUS) prostatic imaging device, have recently been added to DRE as tools for the possible early detection of the disease^{31,33,45-48}. Widespread screening would have an impact on the epidemiology of the disease, resulting in increased detection of early disease^{49,50}. Organisations such as the American and Canadian Cancer Societies have called for mass screening programs but, on the basis of available evidence as to the effectiveness of the screening procedures in reducing mortality from the disease, mass screening is not currently being widely recommended by most credible authorities^{33,36,51-54}. It is possible, however, that many individual physicians will use these new technologies to engage in increased case-finding in their existing patient populations.

Possible Reasons for the Observed Increase in New Cases

There are several possible explanations for the trend seen in age-standardised prostate cancer incidence rates in Canada. The increase could reflect a true increase in the prevalence of as yet undetermined underlying risk factors. Alternatively, improvements in case reporting or in data quality might erroneously inflate rates. Technological advances in the clinical or laboratory setting, or widespread screening for the disease, might be resulting in increased diagnosis of the disease over time. Although these explanations are all plausible many have not been tested, and comments on the role that each may play in the epidemiology of the disease remain largely speculative.

There are other plausible explanations for the trends in rates, many of which have also not been adequately tested, and it is on these that this thesis focuses. The apparent rise in rates could be secondary to increased case finding, i.e., a greater detection of the disease. Figure 2 shows a schematic model of the usual events leading to the histological diagnosis of malignancy in a man with latent or aggressive cancer, and illustrates the points in the continuum where increased case finding could occur over time. Increased detection of earlier stage disease could be the result of changes in patient behaviour resulting in earlier attendance at physician clinics. It could also result from changes in health services, meaning physician practice at a clinical and/or laboratory level, e.g., primary care physicians may be performing more DREs, or be more skilful in interpreting the examinations; urologists may be performing more prostatectomies for relief of bladder outlet obstruction, resulting in greater opportunities for the incidental diagnosis of malignancy; or pathologists may be handling surgical specimens in a way that allows greater diagnosis of microscopic malignancy.

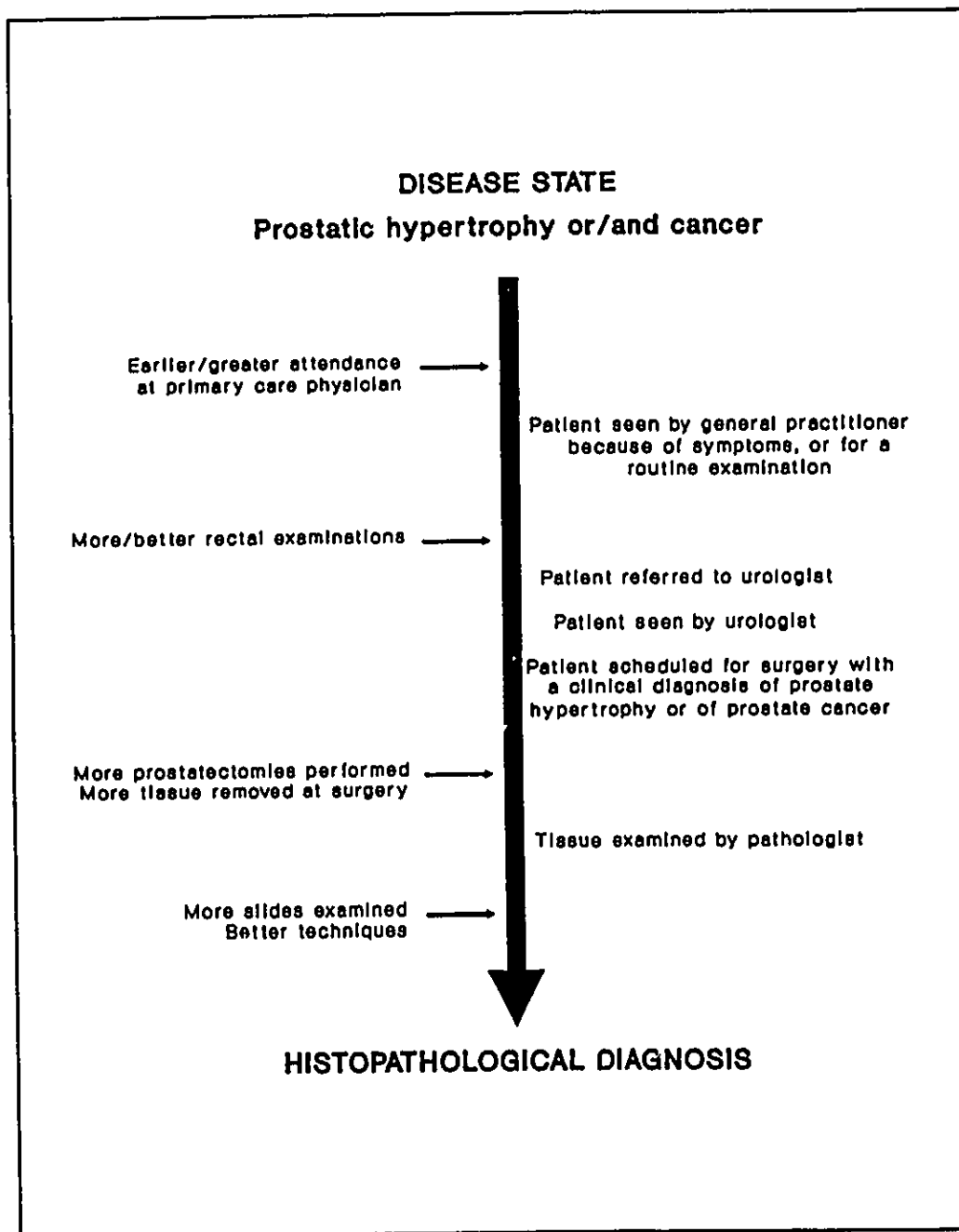


FIGURE 2 A model showing the stages, where increased case finding might occur over time, in the continuum from onset of prostatic disease to the diagnosis of a malignancy

The Public Health Significance of Prostate Cancer and the Contribution of this Work to its Field of Study

The estimated economic burden of illness, disability, and premature death caused by cancer exceeded \$9 billion per year in Canada in 1986⁵⁵. More than \$7 billion dollars (almost 80%) of this amount was due to the indirect costs of premature mortality⁵⁵. Prostate cancer is responsible for 3.5% of all potential years of life lost due to cancer¹, thus being responsible for nearly 250 million 1986 dollars of lost productivity, as well as the direct financial and human costs which result from a diagnosis of this disease. The aging of the Canadian population, combined with the increasing availability of diagnostic and therapeutic technology, suggest that the burden of prostate cancer may increase in the future. However, it remains unclear to what extent the newly diagnosed cases represent a true increased burden rather than an artefactual one.

This issue is relevant to health care planning since a significant portion of the observed increase in incidence rates may be the result of an increase in detection of latent, incidentally discovered tumours with a low tendency to aggressive behaviour. If this is the case, the implications for service planning are that prostate cancer may be a lower priority than if more aggressive tumours are contributing to the observed increase.

National Databases

The existence of high quality data in accessible databases facilitates the study of this question. Three national databases which are available for use in Canada have been used for this thesis. These are The National Cancer Incidence Reporting System (NCIRS), The Canadian Mortality Database (CMDDB) and The National Hospital Morbidity Statistics Database.

The National Cancer Incidence Reporting System (NCIRS)

Canada is one of few countries in the world with a national cancer registry that covers the whole population. The NCIRS was established in 1969, and, with the inclusion of Quebec in 1970, the entire country's population was covered²⁵⁶. The NCIRS is operated and maintained at the Canadian Centre for Health Information, at Statistics Canada. Each provincial or territorial cancer registry reports new primary sites of cancer occurring among its residents to the registry. Provincial and territorial registries obtain incidence information from seven main sources (See Appendix A), and although no single source is used by all 12 registries, most use treatment records of cancer patients, haematological or histological reports from pathology laboratories, and death certificates. Some registries also receive information from hospital separation records, autopsy reports, and medicare files.

Incidence is collected as a function of the "province of residence", irrespective of the place of diagnosis of the cancer.

The Canadian Mortality Database (CMDB)

All death certificates in Canada are maintained on file in the Health Status Section of Statistics Canada. Each province or territory supplies Statistics Canada with a compilation of registrations and national data have been available since 1921⁵⁷. The CMDB is a computer file of the records of death events since 1950⁵⁸.

Mortality is collected as a function of the "province of residence", irrespective of the place of death.

The National Hospital Morbidity Statistics Database

This database was established in 1960, and is maintained by the Canadian Centre for Health Information, at Statistics Canada. Acute care, convalescence and chronic care hospitals across the country complete an admission/separation form each time an individual is admitted to the hospital. Surgical procedures performed during the given admission (or "separation") have been recorded on this form since 1968. Each Provincial Hospital Insurance Commission, or equivalent for non provincial hospitals, supplies Statistics Canada with the hospital separation records for its jurisdiction. The use of administrative data ensures that the database is 100% complete for all hospitals, with the exception of National Defence and Worker's Compensation hospitals, as it supplements the Hospital Medical Records Institute (HMRI) database in those provinces where it is incomplete. Statistics Canada prepares a standard record to eliminate variability between the provinces in the content and format of information⁵⁹, and publishes various morbidity reports,

including one relating to surgical procedures⁶⁰.

Unlike incidence and mortality statistics, hospital morbidity is collected as a function of the "province of hospitalization", not the "province of residence". Care must therefore be taken when making interprovincial comparisons⁵⁹. However, less than two percent of all hospital separations involve patients who are not residents of the reporting province⁶¹.

AIMS, OBJECTIVES AND HYPOTHESES

The purpose of the thesis was to examine the occurrence of prostate cancer in Canada.

Aims

- i) To describe the temporal and geographic trends in prostate cancer incidence and mortality in this country.
- ii) To explore the possibility that changes in incidence are associated with earlier detection of disease.
- iii) To explore the possibility that changes in incidence are associated with changes in health services.

Objectives

- i) To obtain age-standardised incidence and mortality rates of cancer of the prostate in Canada for a period of at least ten years, and for the provinces of Canada for a one year period.
- ii) To obtain age-standardised rates of prostatectomies in Canada for a period of at least ten years, and for the provinces of Canada for a one year period.
- iii) To assess the association between prostate cancer incidence rates and prostatectomy rates in Canada.
- iv) To obtain clinical information relating to patients diagnosed with

prostate cancer in two time periods, at least ten years apart, and to assess differences in the stage distribution of incident cancers, and in the circumstances leading to the diagnosis of cancer.

- v) To obtain information relating to the handling of histopathological laboratory specimens of prostate tissue during two time periods, at least ten years apart.

Hypotheses

The null hypotheses established, *a priori*, for statistical significance testing were that:

- i) there is neither a temporal nor a spatial correlation between incidence rates of prostate cancer and rates of prostatectomy in Canada.
- ii) in samples, from two time periods ten years apart, of men diagnosed with incident prostatic cancer:
 - a) there is no change in the distribution of clinical stage at diagnosis (i.e. the distribution of latent, localised or invasive disease).
 - b) there is no change in the proportion of patients diagnosed following a suspicion of cancer being aroused at routine examination by a primary care physician.
 - c) there is no change in the proportion of patients diagnosed incidentally after surgery for suspected BPH.

- iii) in samples, from two time periods ten years apart, of men undergoing prostatectomy there is no change in the number of histological slides examined by pathologists per 10 grams of tissue submitted, irrespective of whether the diagnosis which is ultimately made is one of benign or malignant disease.

METHODS

Design

The investigation comprised four parts:

- i) A descriptive analysis of Canadian mortality and incidence data for prostate cancer, and of prostatectomy data.
- ii) An ecological study of the correlation, over time and in space, between the age-standardised incidence rates of prostatic cancer and of TURPs in Canada.
- iii) A quasi-experimental analysis of the changes, over time, in the distribution of clinical stage at diagnosis, and in the process leading to the diagnosis.
- iv) A quasi-experimental analysis of the changes, over time, in the handling of surgical pathology prostatectomy specimens in the histopathology laboratory.

Ethical Considerations

Only aggregate data were obtained from the Canadian Mortality Database, the National Cancer Incidence Reporting System, Statistics Canada census publications, and the National Hospital Morbidity Statistics Database. Unique identifiers had been removed, and individual identification was impossible.

Approval to undertake the hospital chart reviews was obtained from the Research

Ethics Committee of the Department of Research, Ottawa Civic Hospital. Individual identifiers were not required for this work, and so the integrity of patient confidentiality was maintained throughout the chart review process.

Age-standardised Incidence and Mortality Rates

Sources of data

Data relating to prostate cancer (International Classification of Diseases, or ICD, Code 185 for both versions 8⁶² and 9⁶³) incidence and mortality were obtained from the NCIRS and the CMDB, respectively, for years 1969 to 1988. Population data were derived from census counts for census years (1971, 1976, 1981, 1986). Intercensal or postcensal estimates were used for the remaining years⁵⁴⁻⁶⁶.

Analysis

Annual prostate cancer mortality and incidence rates were calculated by five year age groups for Canada and the provinces, and age-adjusted by the direct method using the 1981 Canadian population as the standard (see Appendix B). Trends were modelled using linear regression of the logarithm of the rates on calendar year in order to quantify the average rates of change over time. This model assumes constant rates of change in the mortality and incidence rates, and the rates of change were calculated from the regression coefficients for each model.

Assessment of an Association Between Incidence Rates and Rates of Transurethral Prostatectomies

Sources of data

The numbers of all prostatectomies (TURPs and all other types) performed each year in Canada and in each of the provinces from 1970 to 1987 were obtained from the National Hospital Morbidity Statistics Database. Procedures in the database were coded according to the International Classification of Diseases Procedures codes (Version 8⁶²) until 1978, and according to the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures codes⁶⁷ from 1979 (see Appendix C for the relevant codes). Population data were again extracted from Statistics Canada census publications^{64,65}.

Analysis

Annual rates of prostatectomies were calculated by five year age groups for Canada and the provinces, and age-adjusted by the direct method using the 1981 Canadian population as the standard (See Appendix B). The trends in rates were modelled using linear regression of the logarithm of the rates on calendar year in order to quantify the average rate of change over time. This model assumes a constant rate of change in the prostatectomy rates and this rate of change was calculated from the regression coefficient.

Scatter plots of the Canadian and provincial TURP rates on the Canadian and

provincial prostate cancer incidence rates were constructed, and correlation coefficients were calculated.

Assessment of the Changes in Clinical Stage at Diagnosis, and in the Process Leading to the Diagnosis

Sources of data and sampling method

Data were collected by reviewing charts of patients diagnosed with prostate cancer during 1976, 1986 and 1987 and discharged from the Ottawa Civic Hospital during the same years.

For each period a list of all patients discharged from the hospital with an HMRI diagnosis of prostate cancer was obtained through the hospital's records department. The list was generated using the hospital discharge records' diagnostic field, seeking an ICD code of 185 in any of the HMRI categories ('most responsible', 'primary', or 'secondary'). This list comprised the sampling frame.

For 1976, all available charts were reviewed. 135 charts, of 145 recorded discharges, could be found (93%). For 1986 all charts which were available were reviewed. However, of 165 recorded discharges, only 99 were available. Sixty-six charts had been sent for microfilming and had not returned with the others. This was not for systematic reasons (e.g. all the thicker charts, etc), but rather was related to apparently random procedural issues in the records department (i.e. certain shelves

of charts were being microfilmed at certain times). An additional 50 charts from 1987 discharges were selected through a systematic sampling procedure, in order to reach the desired sample size.

A total of 284 charts were initially reviewed to exclude miscoded cases (of which there were 3 in the 1976 sample and 5 in the 1986/7 sample), or those in whom the diagnosis was not made during the year of the given admission (57 in 1976, and 44 in 1986/7). The resultant comparison groups comprised 75 cases diagnosed in 1976 and 100 diagnosed in 1986 or 1987.

Reason for restricting study to charts of men in whom the diagnosis was made during the year of the admission

The relevant comparisons between the two time periods relate to characteristics of incident cases. However, the sampling frame available was based on hospital discharges, and the given admission may not have been the first for the individual with the diagnosis of prostate cancer. It was not possible to select all patients diagnosed in the hospital in a given year without contaminating the sample with those diagnosed in previous years, but admitted for a new problem, or a complication, in the year of interest. Therefore more charts had to be reviewed than could be used in the analysis. If all charts had been used for the analysis the sample would have been biased with "prevalent" cases, admitted and discharged in the year of interest, but actually diagnosed in earlier years. Thus only charts from patients in whom the diagnosis had been made in the same year as the admission

were used for the study.

Sample size considerations

The sizes of the samples of charts selected were calculated to be able to detect, with 80% power, a 20% absolute rise in early stage disease. This degree of increase was arbitrarily determined.

For the purposes of the calculation the null hypothesis was that the proportion of stage A or B disease in the sample populations in 1986 would be the same as that in 1976. In appendix D the size of each sample required to detect a difference of 20% in the proportion of stage A or B tumours (e.g. from 20% in 1976 to 40% in 1986) is shown, as is the formula for the comparison of two proportions⁶⁸. α was set at 0.05.

Previous work⁶⁹ has shown that in the 1970's the proportion of prostatic cancer which was diagnosed at stage A or B was in the region of 50% in the United States. Assuming a comparable figure for the same time period in Canada it was determined that the required sample size was 93 charts in each group. To account for anticipated exclusions (miscoded cases, "prevalent" cases) the desired sample size was increased by 50%, to 140 in each time period.

Variables

An information sheet, shown in Appendix E, was used to obtain data from each

chart.

For each patient, in addition to age and place of residence at the time of first diagnosis, information was collected to characterize the clinical staging of the disease and the process that led to the diagnosis of malignancy.

For staging purposes a modified Whitmore-Jewett staging system⁷⁰, was used, where stage A indicates non-palpable latent, incidentally discovered disease (with no evidence of any invasion on subsequent staging), stage B indicates palpable but localised disease (confined to the prostatic capsule), and stages C (regional invasion) and D (metastatic spread) indicate invasive disease. A stage was assigned to each patient based on the clinical, surgical, and/or pathological records present in the chart for the admission during which the diagnosis was first made. Typically the charts contained results of clinical examinations, laboratory investigations (e.g. X-rays, CT scans, lymphangiograms, bone scans, serum alkaline phosphatase levels, etc) and pathological investigations (e.g. surgical specimen histopathology, pleural fluid cytology, etc).

The information pertaining to the process that led to the diagnosis of malignancy that was sought included the presence or absence of symptoms at the time of presentation, the process whereby the physician became alert to the possible presence of malignant disease, and the first diagnostic procedure used to obtain tissue for histological diagnosis of malignancy. Patients presented with one of three

clinical pictures:

- i) **"Routinely detected"** - the disease was asymptomatic, and evidence of prostatic cancer was detected during the course of DRE for a routine physical or unrelated medical problem; the suspected diagnosis was then confirmed by obtaining prostatic tissue for histological examination.
- ii) **"Symptoms.Expect BPH"** - the patient had symptoms of prostatism but there was no clinical reason to suspect cancer. BPH was suspected and malignancy was diagnosed incidentally during routine histological examination of tissue obtained during prostatectomy.
- iii) **"Symptoms.Expect Ca"** - the patient had symptoms and/or signs leading the primary care physician to suspected cancer. Histological confirmation was effected on tissue derived from a prostatectomy procedure, or from a needle biopsy.

Other information captured related to the place of first diagnosis, and the histological type of tumour. For those cases in whom a latent cancer was diagnosed following prostatectomy for putative BPH, information was also obtained as to the amount of prostatic tissue submitted to the histopathology laboratory, and the number of slides produced for examination (see below).

Analysis

Statistical analyses was performed using EPIINFO 5 software. Frequencies were obtained for each variable, and proportions of latent, localized, and invasive disease were computed for each time period, as were proportions of symptomatic and non-symptomatic patients, and suspected and unsuspected disease. Multiplication of these proportions by the average age-adjusted prostatic cancer incidence rate for the Ottawa-Carleton census division in the years 1975-77 and 1985-87 was performed to obtain estimates of selected variable-specific incidence rates in the community during the two time periods. Characteristics of the cases were assumed to be generalisable to the main geographic area served by the hospital (the Ottawa-Carleton census division), and this allowed for the extrapolation of observations from the sample to estimate age-adjusted population rates. Evidence for the validity of the assumption of generalisability was sought by comparing age distributions of the sample cases with those of all residents of Ottawa-Carleton diagnosed with prostate cancer in each time period (see results section). The legitimacy of extrapolating observations from the sample to the Ottawa-Carleton population is based on the further assumption that the proportion of the variable for which variable-specific rates are being estimated in the Ottawa-Carleton population is the same within each age group in the sample. This assumption was tested for each of the relevant variables in each time period, using three age groupings, and was proven to be valid. An example of the procedure is shown in Appendix F.

Postal codes were used to define the patient's place of residence as being within or outside of the Ottawa-Carleton census division. The Ottawa-Carleton census division corresponds with the boundaries of the regional municipality of Ottawa-Carleton, which did not change between 1976 and 1986. The Postal Code Conversion File⁷¹, developed by Statistics Canada, was used to convert the patient's postal code to a census division. This file uses the Canada Post Forward Sorting Area (FSA), which is the first three letters/digit of the postal code, to define the census division (see Appendix G)⁷². Changes in FSA classification in Ottawa-Carleton between 1976 and 1986 occurred, but only in marginal FSAs in which few sample patients lived. These changes were, therefore, disregarded for the purpose of the analysis.

For some patients information contained in the charts was insufficient to obtain all the variables of interest. In order not to lose the information which was available from these charts missing values were excluded from variable specific analyses, rather than excluding the entire set of variables for such cases. The number of missing values was never more than 6 out of 175 (or 3%), and, therefore, sensitivity analyses were not performed.

Statistical significance was tested using the z test for comparisons of proportions in the sample (simple binomial), and for comparison of the estimated variable-specific

rates in the Ottawa-Carleton population (compound binomial^a).

Assessment of the Changes in the Handling of Prostatectomy Specimens in the Histopathology Laboratory

Sources of data and sampling method

Pathology records were examined in all the above mentioned charts in which patients had been diagnosed as suffering from malignant prostatic disease following prostatectomy for what had been a suspected BPH.

In addition, random samples of the pathology records of all cases diagnosed at the Ottawa Civic Hospital, after TURP, as BPH in 1976 and in 1986 were reviewed to obtain similar information. For each year a list of all patients in whom a pathological diagnosis of BPH had been made was obtained through the hospital's Department of Pathology. The list was generated using the records' topography and morphology fields. The coding systems used by the Department of Pathology for record keeping were the SNOP system (Systematized Nomenclature of Pathology)⁷³ for 1976, and the SNOMED system (Systematized Nomenclature of Medicine)⁷⁴ for 1986 (See Appendix C for the relevant SNOP and SNOMED codes). This list comprised the sampling frame, and records were selected through a systematic procedure, in order to reach the desired sample size.

^a For variable-specific estimates of population rates the variance of the difference between estimates for the 2 time periods comprise components due to both the variance in the hospital sample and the variance in the population rates.

A total of 247 records were selected, 115 from 1976 and 132 from 1986. This represented one third of records for 1976 and one quarter of those for 1986. 100% of records were available for review.

Sample size considerations

The samples selected were calculated to be able to detect, with 80% power, a 10% increase, between the two time periods, in the number of slides examined per gram of tissue submitted. This degree of increase was arbitrarily determined, as an increase of 0.1 slides per gram submitted, or 1 slide per 10 grams.

The sample size required was estimated by applying the formula for the comparison of two means^{b,68}. For the purposes of the calculation the null hypothesis was that the number of slides examined per gram of tissue submitted in 1986 would be the same as that in 1976. α was set at 0.05.

Since no previous work of this sort had been undertaken 20 records from 1976 were initially reviewed, to obtain an estimate of the expected variance of the variable of interest. The mean value was 0.26 slides per gram, with a standard deviation of 0.26. Using this standard deviation in the sample size calculation it was determined that the required sample size was 106 records in each group.

^b The formula for the comparison of two means is:

$$n \text{ (in each group)} = 2\sigma^2(Z_\alpha + Z_{\beta})^2 / [\mu_2 - \mu_1]^2$$
 where σ = the standard deviation, and
 μ = the population means

Variables

Information was obtained as to the amount of prostatic tissue submitted to the histopathology laboratory from each surgical procedure, and the number of slides produced for examination. A ratio of slides produced per 10 grams of tissue submitted (slides/10 grams) was calculated.

Analysis

Analyses were performed using the EPISTAT and EPIINFO software packages. Statistical significance was tested using the two-tailed student's *t*-test for testing the difference between means, and the Chi-squared test for comparison of proportions. Analysis of covariance (ANCOVA) was used in the analysis of histopathological data. When employing the student's *t*-test a test for homogeneity of the variances was undertaken, and where there was no homogeneity a non-parametric test of statistical significance (Mann-Whitney test) was used instead of the parametric test. There were no missing values.

RESULTS

Age-standardised Rates and The Association Between Incidence and Transurethral Prostatectomy Rates

Temporal trends

Figure 3 shows age-standardized prostate cancer mortality and incidence rates for all of Canada as a function of time. Between 1969 and 1988 mortality rates increased 23%, at an average annual rate of 1%. During the same period incidence rates increased 71%, or an average of 3% per annum. The rise in prostate cancer incidence has been especially steep since 1976. The ratio of prostate cancer mortality to incidence has decreased steadily from 46% to 33% since 1969.

Age-standardized TURP and total prostatectomy rates for all of Canada from 1970 to 1987 are presented in Figure 4. The proportion of all prostatectomies performed during that time period which were TURPs increased from 81% to 97%. There was an increase in the age-adjusted TURP rate of 55% overall and 2% annually.

Figure 5 shows age-standardized prostate cancer incidence rates and TURP rates as a function of time, and these rates are shown on a scatter plot in figure 6. Modelling using linear regression of the incidence rates on the TURP rates yielded a direct correlation of 0.94 ($p < 0.0001$). This suggests that 88% (r^2) of the variation in incidence is explainable by the variation in TURP rates.

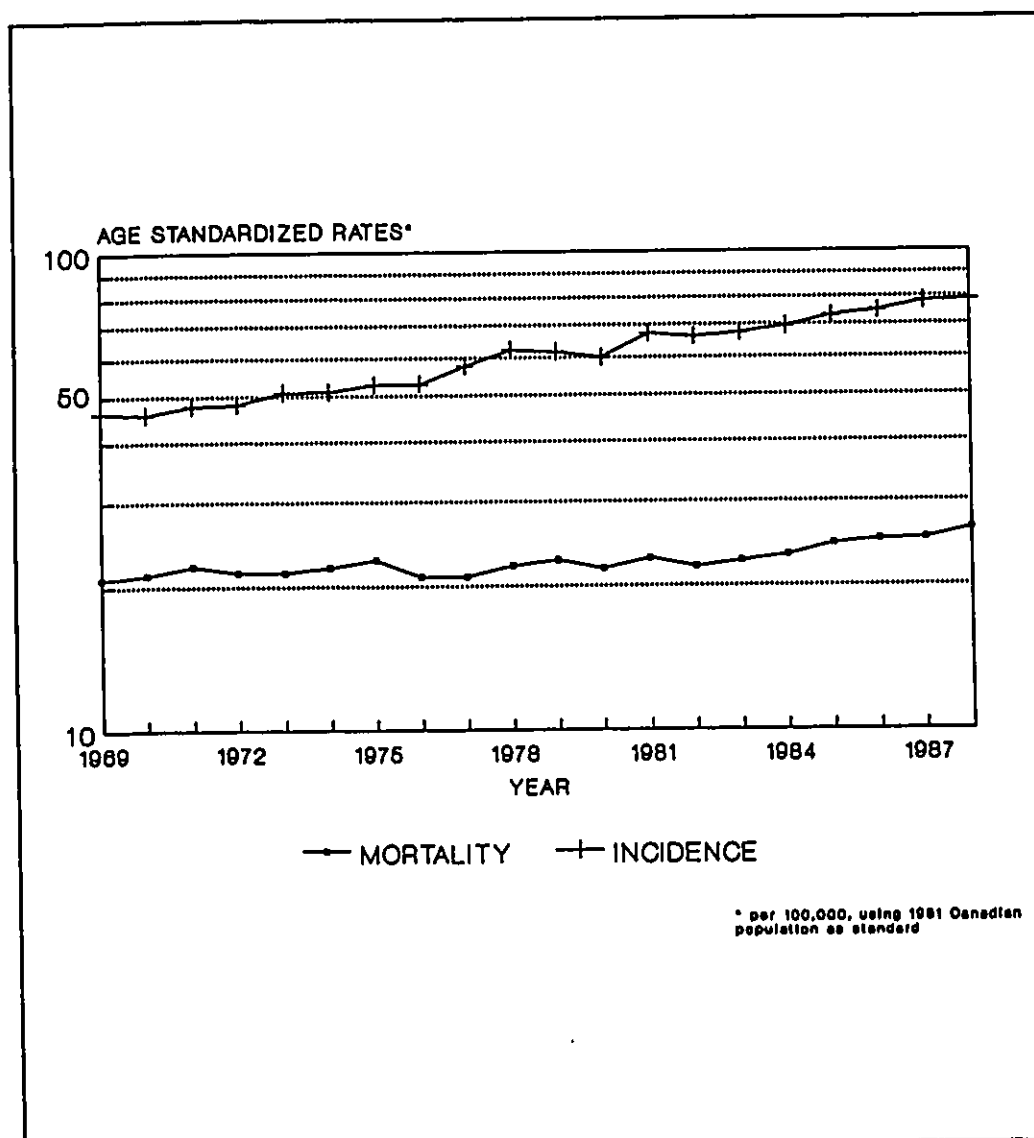


FIGURE 3 Age-standardised prostate cancer incidence and mortality rates for Canada (1969-1988)

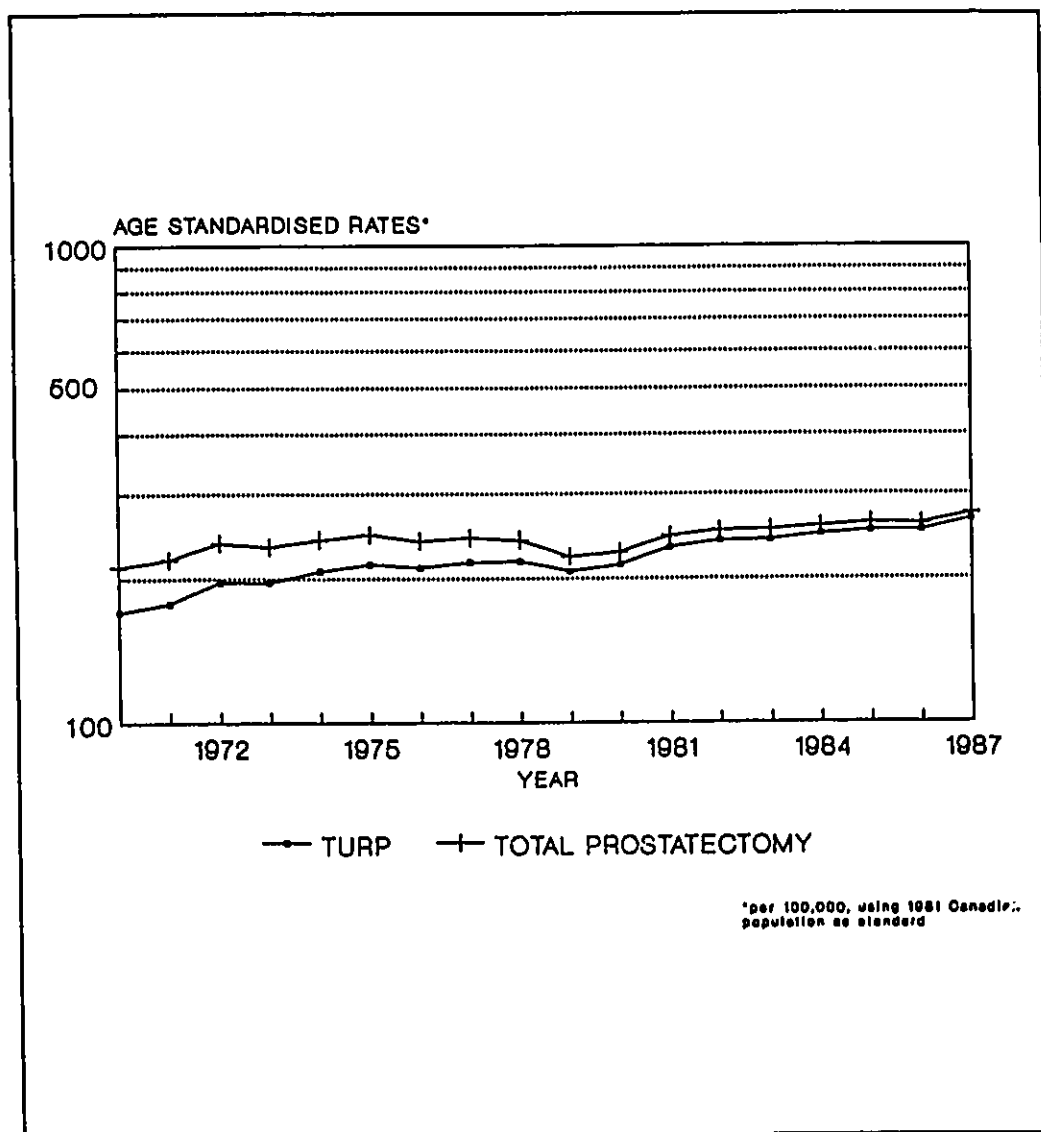


FIGURE 4 Age-standardised prostatectomy rates for Canada (1970-1987)

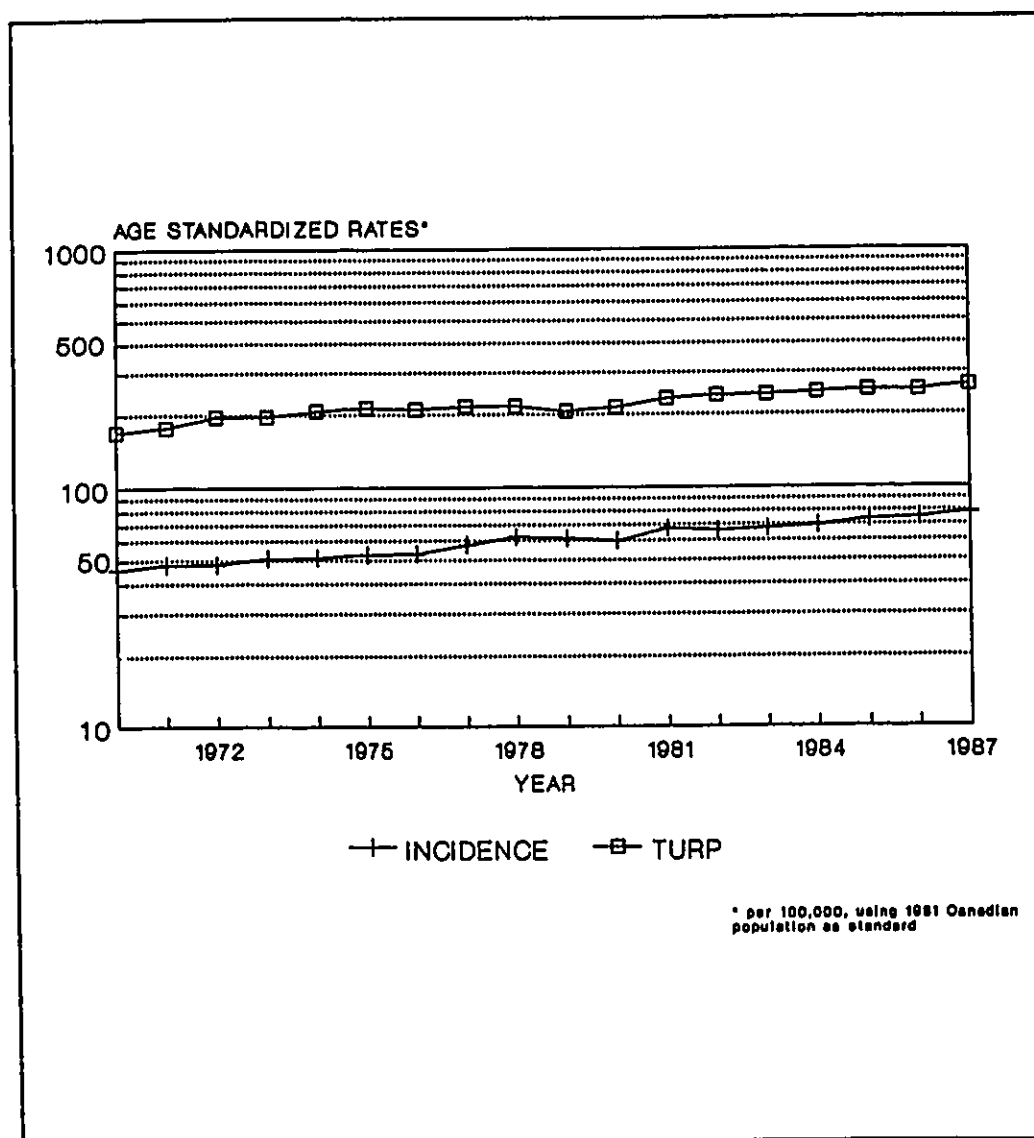


FIGURE 5 Age-standardised prostate cancer incidence and TURP rates for Canada (1970-1987)

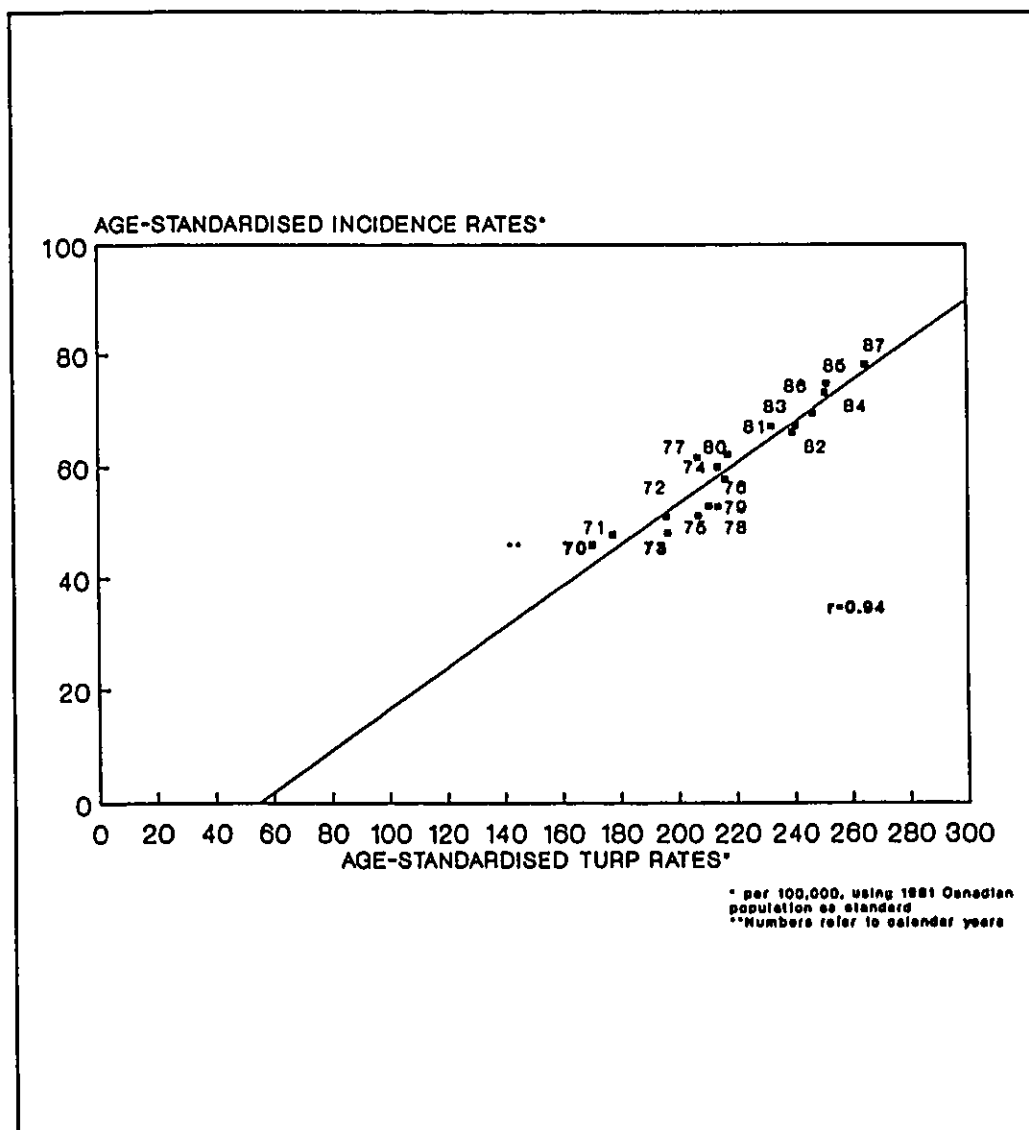


FIGURE 6 Scatter diagram of age-standardised prostate cancer incidence rates on age-standardised TURP rates for Canada (1970-1987)

Geographical trends

Provincial prostate cancer incidence and mortality rates averaged over 1984 to 1986 are presented in Figure 7. Western provinces generally have higher incidence rates, whereas mortality rates are essentially the same throughout the country. Figure 8 shows a linear regression modelling age-standardized provincial prostate cancer incidence rates on TURP rates for 1984 to 1986. This model yielded a direct correlation of 0.72 ($p < 0.001$), suggesting that 52% (r^2) of the variation in incidence is explainable by the variation in TURP rates.

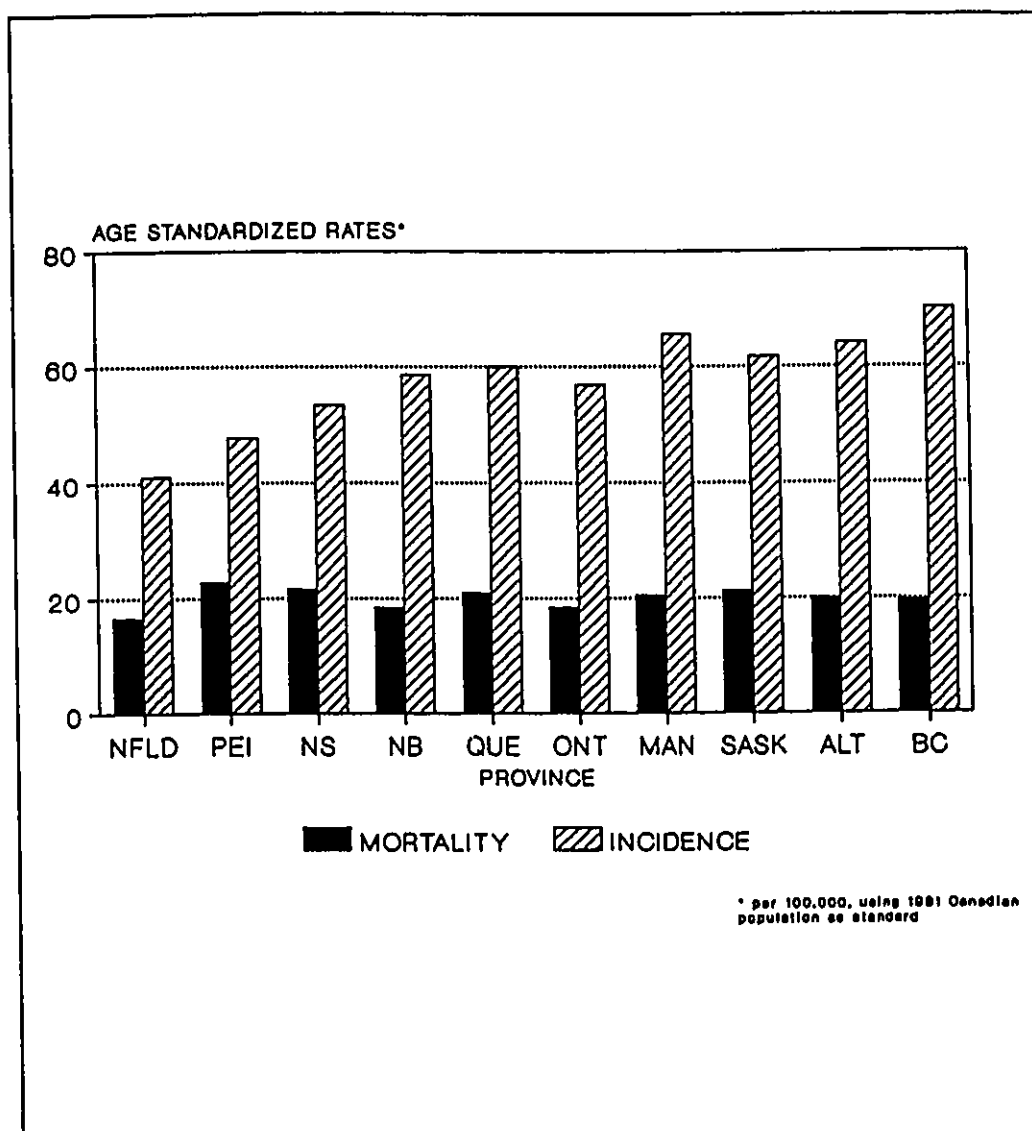


FIGURE 7 Age-standardised prostate cancer incidence and mortality rates for the provinces of Canada (1984-1986)

NFLD=Newfoundland, PEI=Prince Edward Island, NS=Nova Scotia, NB=New Brunswick, QUE=Quebec, ONT=Ontario, MAN=Manitoba, SASK=Saskatchewan, ALT=Alberta, BC=British Columbia

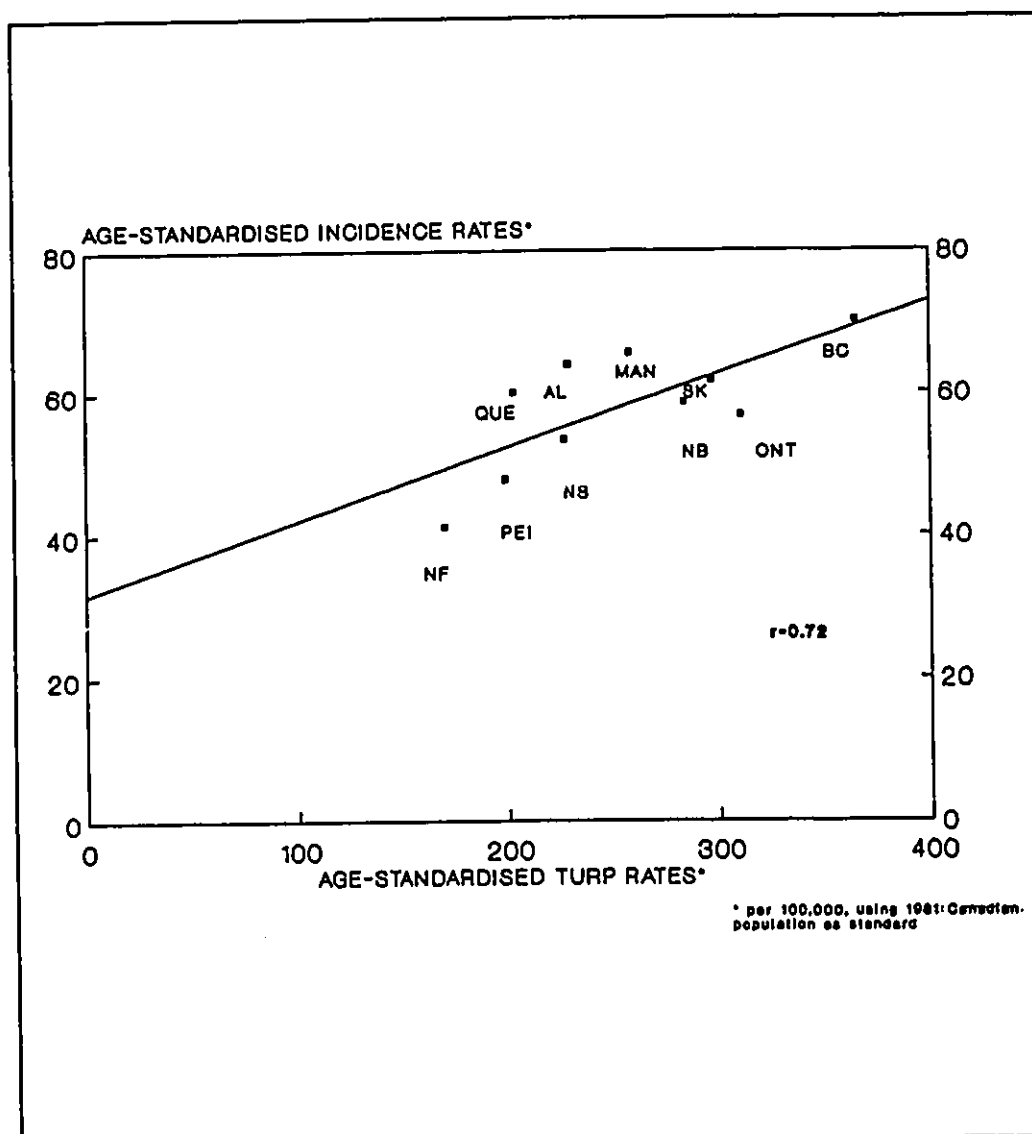


FIGURE 8 Scatter diagram of age-standardised prostate cancer incidence rates on age-standardised TURP rates for the provinces of Canada (1984-1986)

NF=Newfoundland, PEI=Prince Edward Island, NS=Nova Scotia, NB=New Brunswick, QUE=Quebec, ONT=Ontario, MAN=Manitoba, SK=Saskatchewan, AL=Alberta, BC=British Columbia

Assessment of the Changes in Clinical Stage at Diagnosis, and in the Process Leading to the Diagnosis

A total of 95% of the charts selected from 1976 discharges and 98% of those from 1986/7 discharges contained sufficient information from which to assess all the variables of interest. The remaining charts were used to obtain the maximum number of variables possible, and missing values were excluded from the relevant univariate analysis.

In both time periods the proportion of cases initially diagnosed at the Ottawa Civic Hospital was > 90%, allowing confidence in the comparability of available clinical data from the time of first diagnosis. Also, in both time periods 97% of diagnoses were based on histopathological reports, and more than 97% of these cases were adenocarcinomas. All the carcinomas that were not adenocarcinomas were reported as transitional cell carcinomas, arising from the prostatic urethra.

During both of the time periods there were only 8 cases who were diagnosed through a process other than by prostatectomy (whether or not cancer was suspected) or needle biopsy. In the 1976 group there were 2 (2.7%) diagnoses made on clinical grounds, and 1 (1.3%) made incidentally at other surgery. In the 1986/7 group 2 (2%) diagnoses were made on clinical grounds, and 3 (3%) by lymph node or bone marrow biopsy. All these cases, by definition, were at least at a clinical stage B at the time of diagnosis.

Among the 1976 group, 77% of cases lived within the boundaries of the Ottawa-Carleton census division, and this proportion was unchanged among the 1986/7 group. The mean age at diagnosis was 71.5 years in 1976 and 73.1 years in 1986/7. The median age at diagnosis for the same periods was 72 years and 73 years respectively. The age distributions are shown in figure 9, and were not significantly different in the 2 time periods using the unpaired t test ($p > 0.05$); the majority of men were diagnosed in their 60's and 70's in both time periods. The age distributions were also not significantly different, using unpaired t tests, from those of incident cases of prostate cancer: in all Ottawa-Carleton residents during 1975-7 and 1985-7 (see figure 10; $p > 0.05$ in both time periods). During 1975-77 the average age adjusted prostate cancer incidence rate in Ottawa-Carleton was 61.3/100,000, and in 1985-7 it was 72.6/100,000.

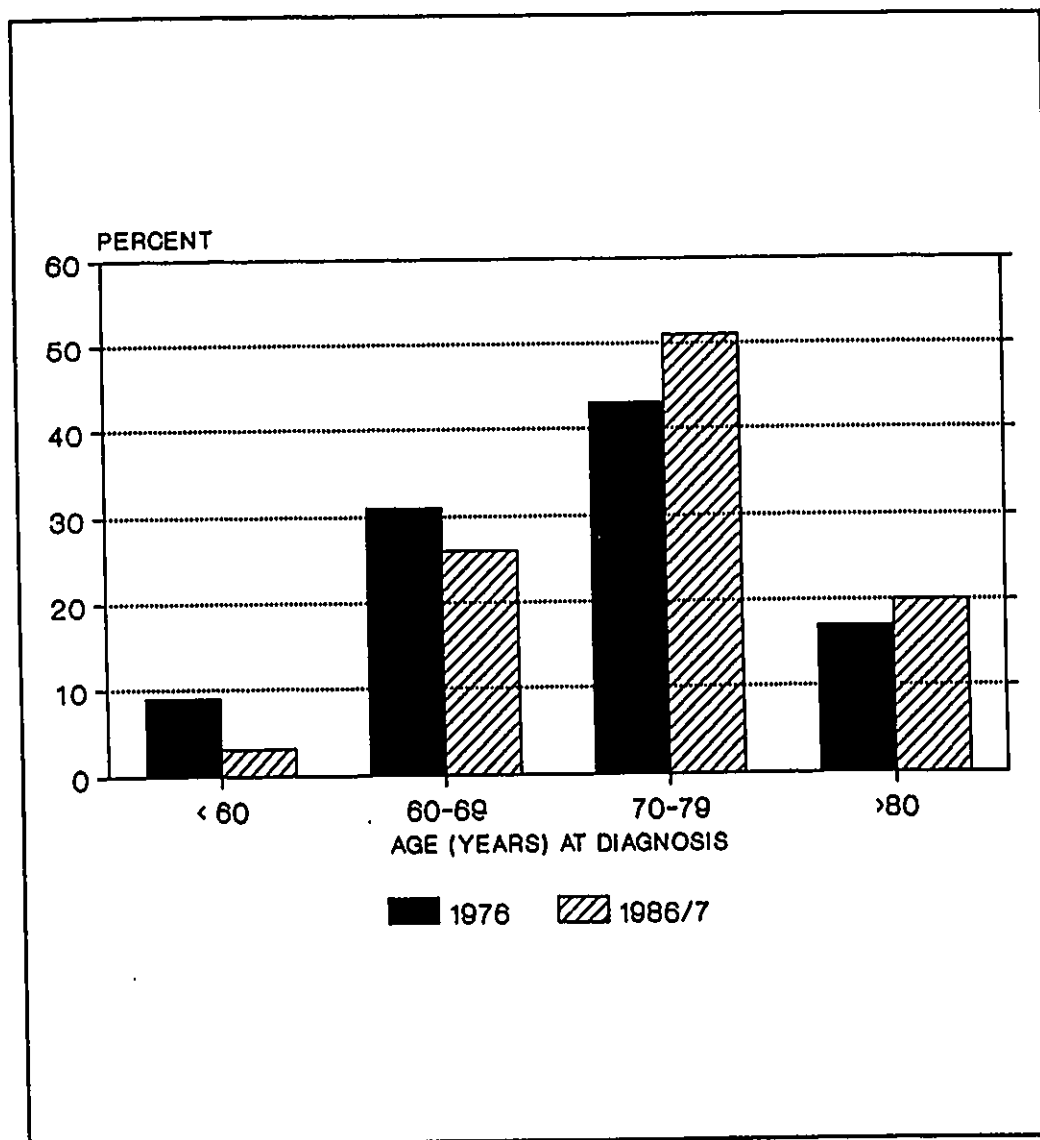


FIGURE 9 Distribution of patient age at time of diagnosis in samples of men with prostate cancer discharged from the Ottawa Civic Hospital in 1976 and in 1986/7

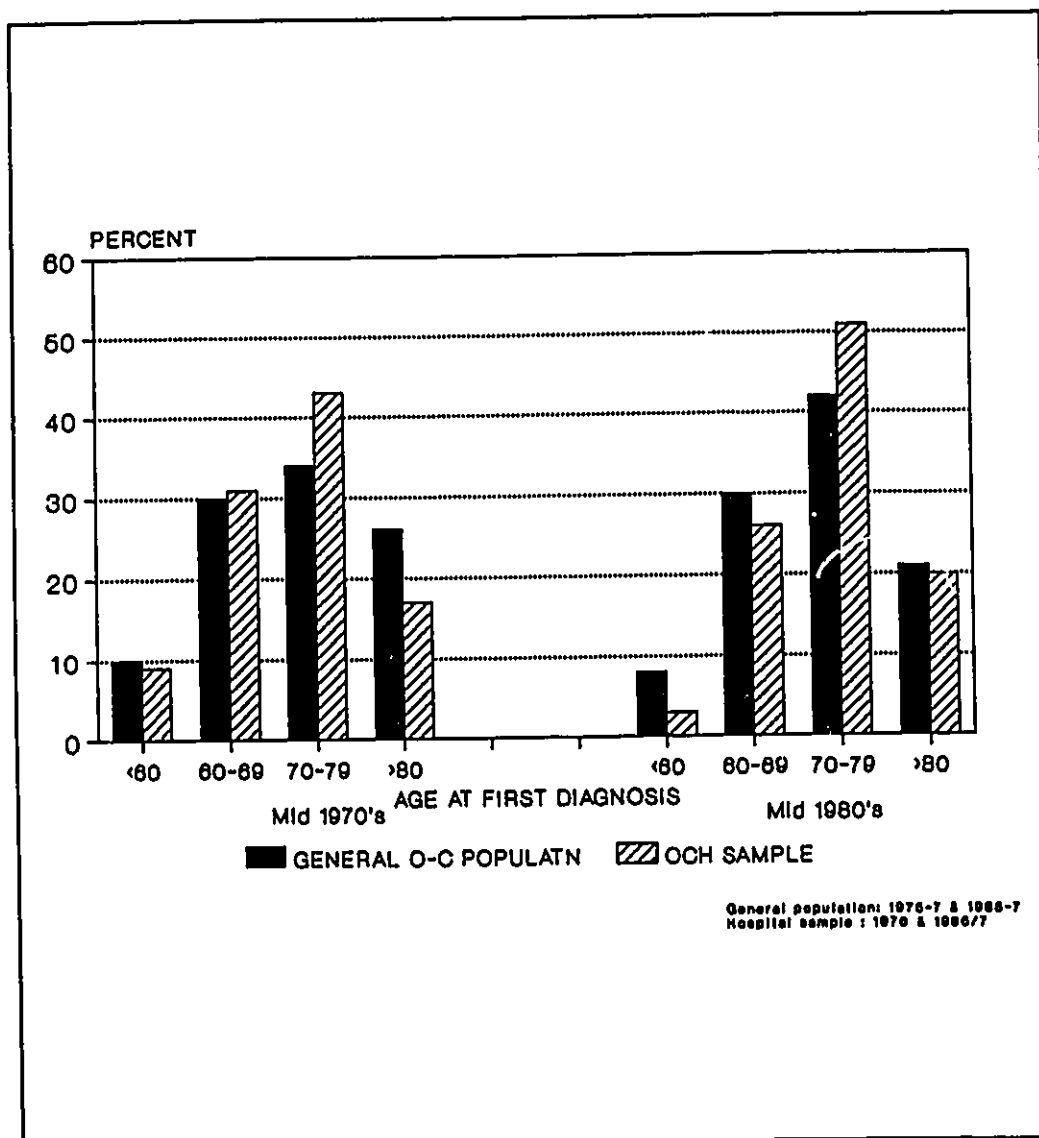


FIGURE 10 Distribution of patient age at time of diagnosis (i) in men with prostate cancer discharged from the Ottawa Civic Hospital and (ii) in all men with prostate cancer residing in Ottawa-Carleton during the mid 1970's and the mid 1980's

Clinical stage

During 1976, 53% of the cancers diagnosed were stages A or B, while during 1986/7 this proportion was 75% ($p < 0.01$). The majority of the invasive cancers were those with distant metastases (stage D) in both time periods.

Categorisation, as shown in Figure 11, of the early stage tumours into latent (stage A) and localised (stage B) disease shows that the increase occurred in both groups. These changes are reflected in significant changes ($p < 0.001$) in estimated stage-specific incidence rates for Ottawa-Carleton based on the sample proportions (Figure 12).

Process leading to the diagnosis

Figure 13 shows the proportions of patients presenting with and without signs and symptoms of malignancy in each time period. Between 1976 and 1986/7 the proportion of cancers diagnosed among men presenting with symptoms and signs of putatively benign disease increased by 11 percentage points, while that in men presenting with suspected malignant disease decreased by 13 percentage points. These differences are not statistically significant, but retrospective calculation of the power to detect a difference in this case showed that this was only 33% at an α level of 0.05^{c,75}.

^c The formula for the power calculation is:

$$Z_{1-\beta} = [\sqrt{N} \cdot (p_2 - p_1) / 2 \cdot \sqrt{PQ}] - Z_{\alpha}$$

where p = proportion in each group
 P = average of proportions

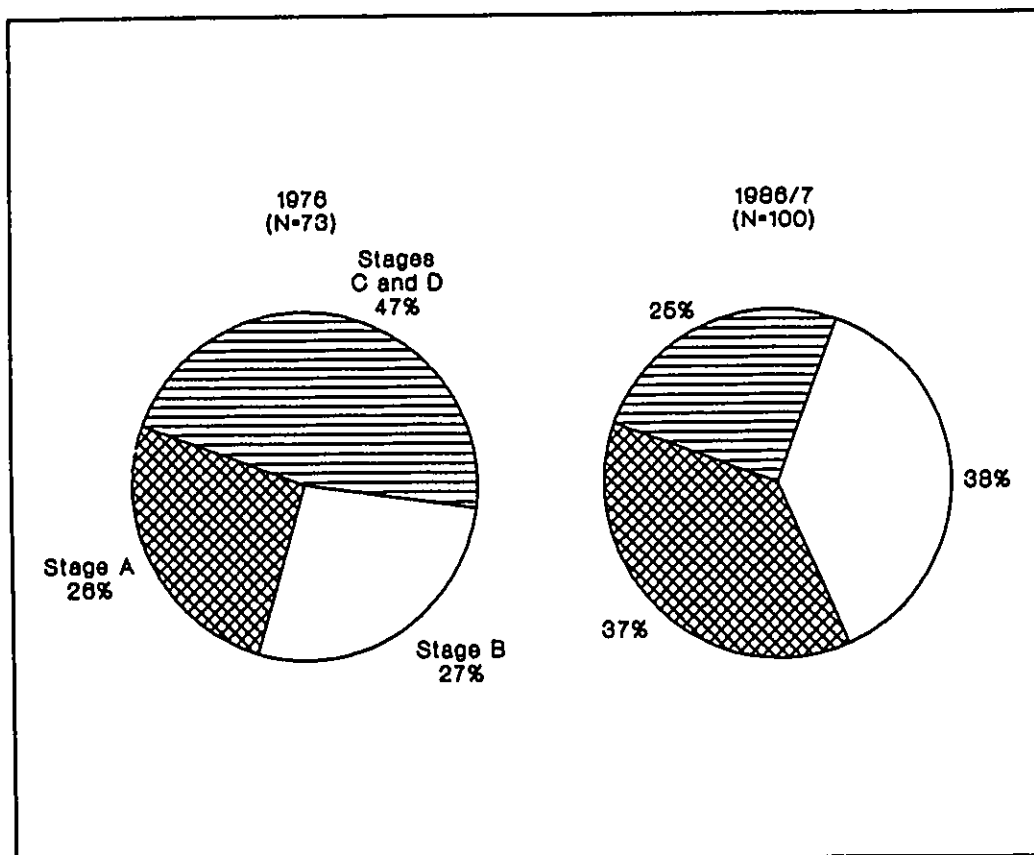


FIGURE 11 Stage distribution of prostate cancer in men who were patients at the Ottawa Civic Hospital in 1976 and in 1986/7

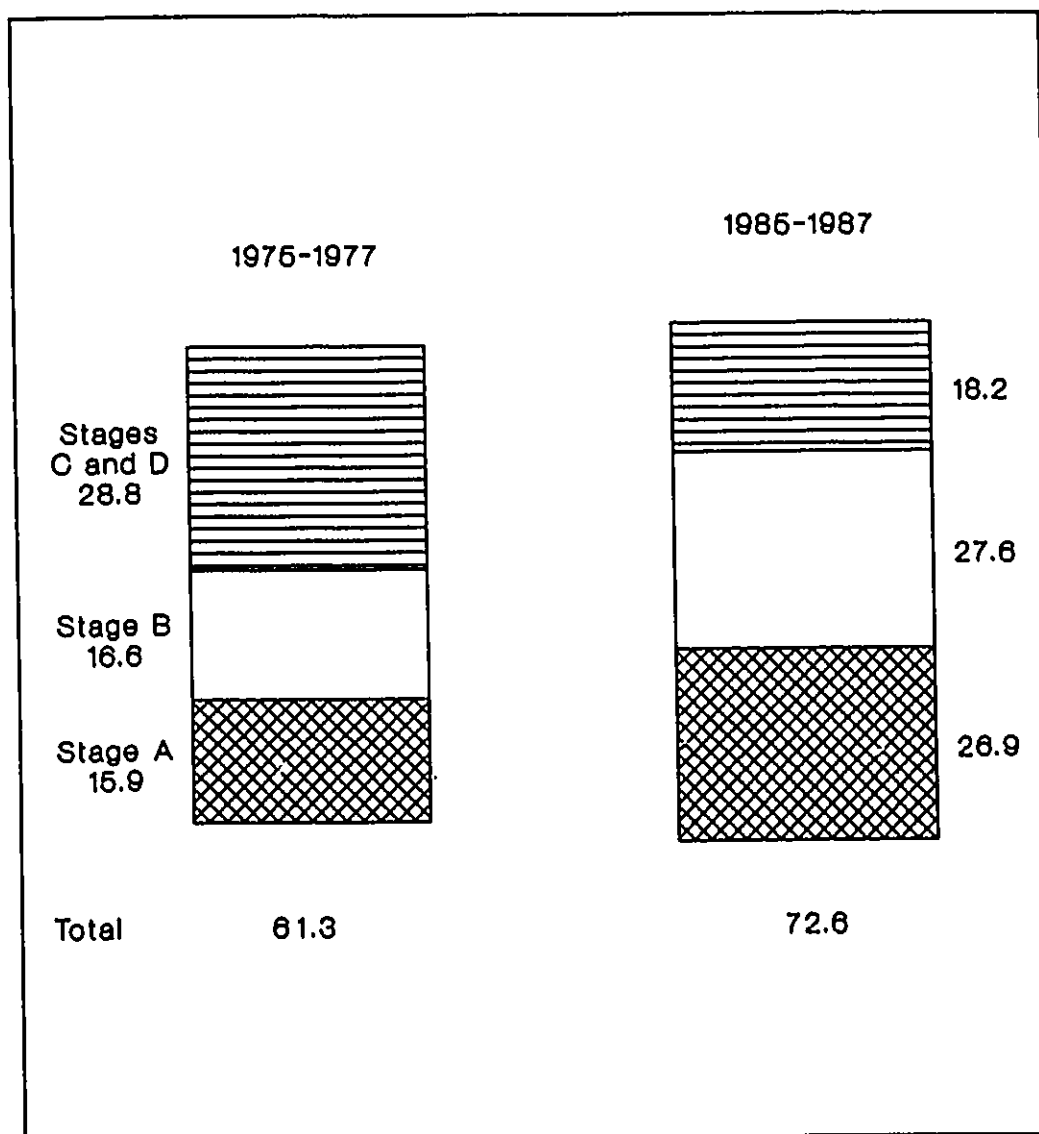


FIGURE 12 Estimated stage distribution of prostate cancer in residents of Ottawa-Carleton for 1975-7 and 1985-7. Rates are per 100,000, standardised to the 1981 Canadian population.

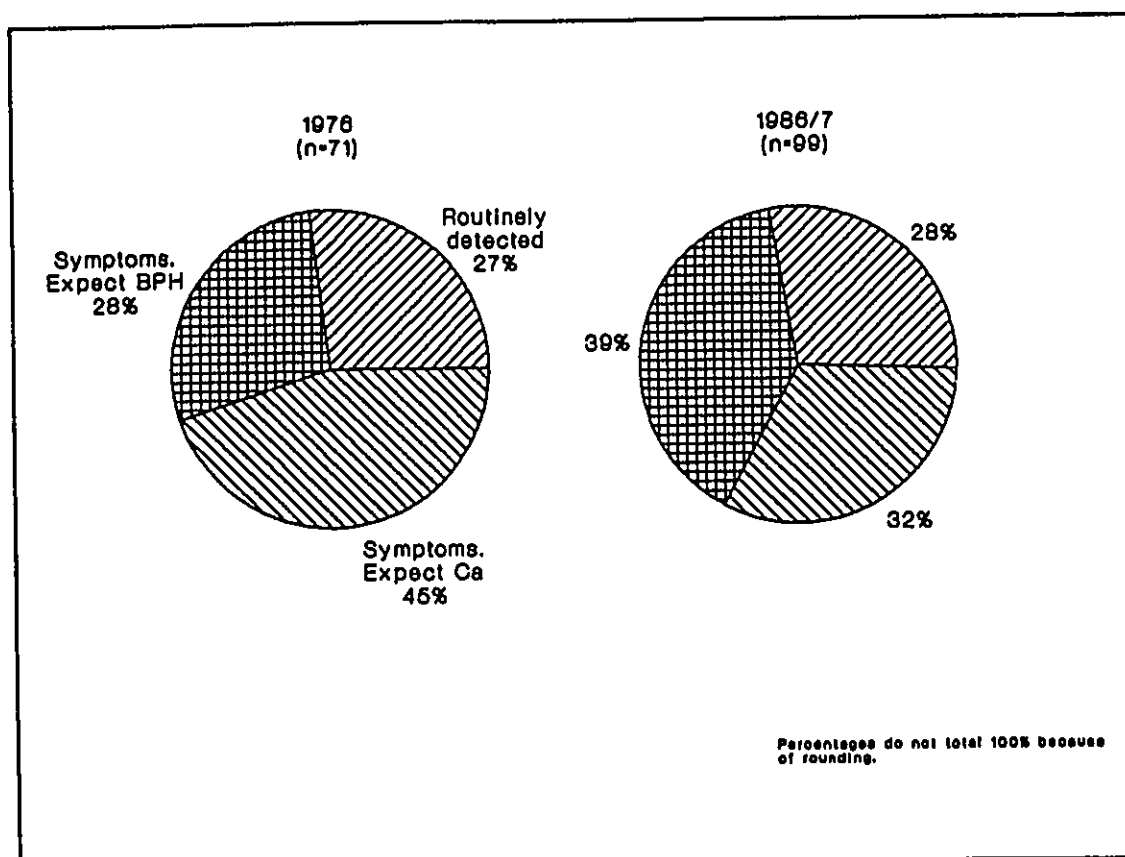


FIGURE 13 Distribution of the circumstances preceding the diagnosis of prostate cancer in men who were patients at the Ottawa Civic Hospital in 1976 and in 1986/7

Two procedures were used to diagnose the majority of prostate cancers, needle biopsy and TURP. A distinction was made between TURPs used in treatment of what was suspected to be BPH and TURPs used in the detection of suspected cancer (or "targeted TURPs"). The proportion of cancers diagnosed incidentally following TURP specifically for suspected BPH increased by 11 percentage points between the two time periods (see figure 14). This change was not statistically significant, but, again, the power to detect a difference was retrospectively calculated at approximately 33%. The increase is consistent with the increase in the proportion of symptomatic patients suspected of having BPH.

During the two time periods the number of TURPs performed at the Ottawa Civic Hospital was essentially the same (551 in 1976 and 542 in 1986/7). The number of urologists working at the hospital decreased by one, from eight to seven, between these two time periods.

Figure 15 shows estimated incidence rates for Ottawa-Carleton, by circumstances preceding the diagnosis of cancer, based on the sample proportions. Most of the significant ($p < 0.05$) increase occurred in patients in whom BPH was suspected and cancer diagnosed incidentally at pathological examination (Symptoms. Expect BPH); there was a smaller increase in asymptomatic patients in whom a suspicious lesion was found at clinical examination (routinely detected).

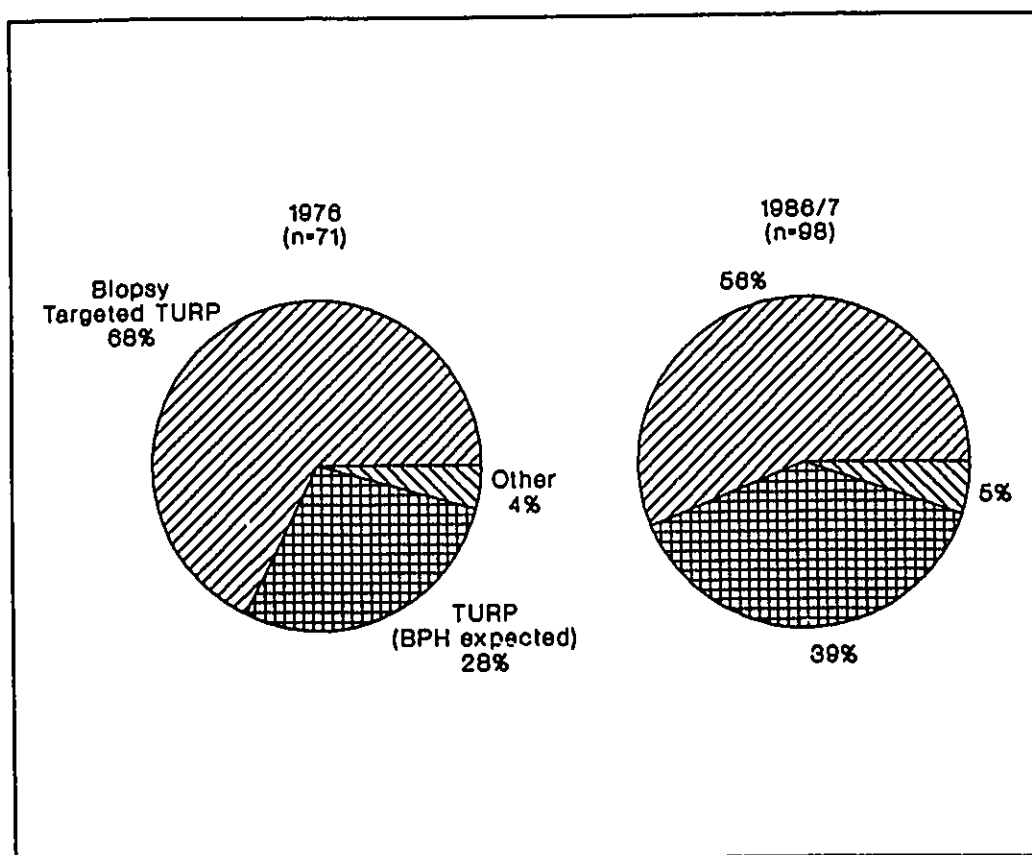


FIGURE 14 Distribution of the procedure used to obtain tissue first for the diagnosis of prostate cancer in men who were patients at the Ottawa Civic Hospital in 1976 and in 1986/7

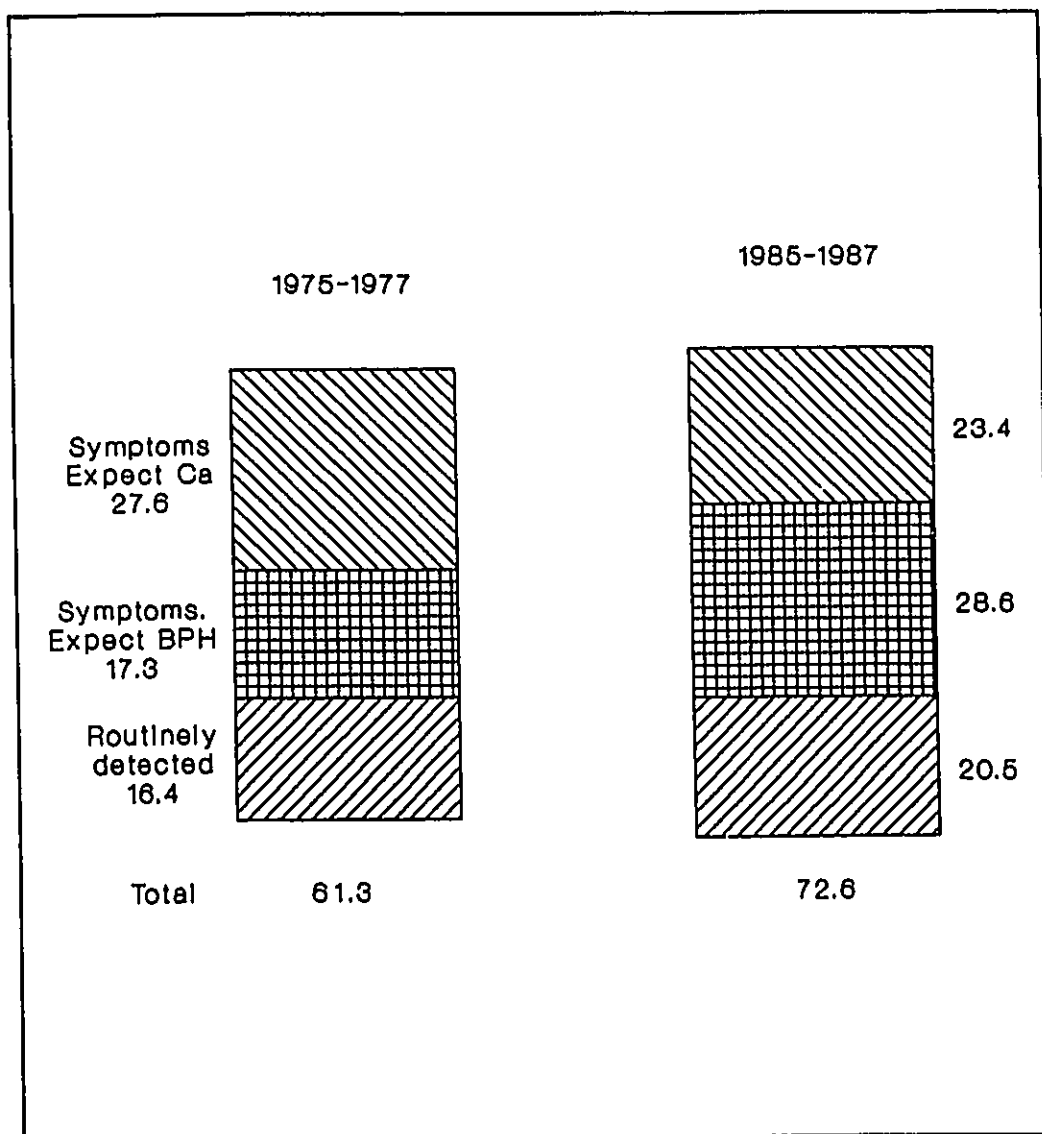


FIGURE 15 Estimated distribution of the circumstances preceding the diagnosis of prostate cancer in residents of Ottawa-Carleton for 1975-7 and 1985-7. Rates are per 100,000, standardised to the 1981 Canadian population.

A subgroup analysis of those patients who had been diagnosed following routine examination and those who had presented with prostatic symptomatology and signs of malignant disease (ie. those not diagnosed incidentally at TURP for BPH) is presented in Table 1. In both subgroups there was an increase in localised disease and a concomitant decrease in [~]invasive disease, but this change was not statistically significant in either case.

TABLE 1: Stage distribution in patients at the Ottawa Civic Hospital in whom cancer was detected following suspicion after routine examination (ROUTINELY DETECTED), and following *a priori* suspicion (SYMPTOMS. EXPECT CA)

	ROUTINELY DETECTED		SYMPTOMS EXPECT CA	
	1976 (n=18)	1986/7 (n=27)	1976 (n=31)	1986/7 (n=32)
LOCALISED DISEASE	67% (n=12)	81% (n=22)	26% (n=8)	50% (n=16)
INVASIVE DISEASE	33% (n=6)	19% (n=5)	74% (n=23)	50% (n=16)

The estimated incidence rates for Ottawa-Carleton, by the procedure first used to obtain tissue for histological diagnosis, are shown in figure 16. Virtually all of the increase in age-standardised rates between 1975-7 and 1985-7 can be explained by the increase in the rate of cancers diagnosed incidentally following TURP for putative BPH. This increase is statistically significant ($p < 0.05$).

Assessment of the Changes in the Handling of Specimens in the Histopathology Laboratory

Tables 2 and 3 show comparisons, between the two time periods, of the mean number of slides examined in the laboratory, the mean mass of prostatectomy specimens submitted to the laboratory, and the mean number of slides examined per 10 grams of tissue submitted. Table 2 shows this information for the cases diagnosed as having BPH, while table 3 shows it for those cases, in the cancer sample, in which patients had been diagnosed as suffering from malignant prostatic disease following prostatectomy for what had been a suspected BPH (i.e., cases of latent cancer).

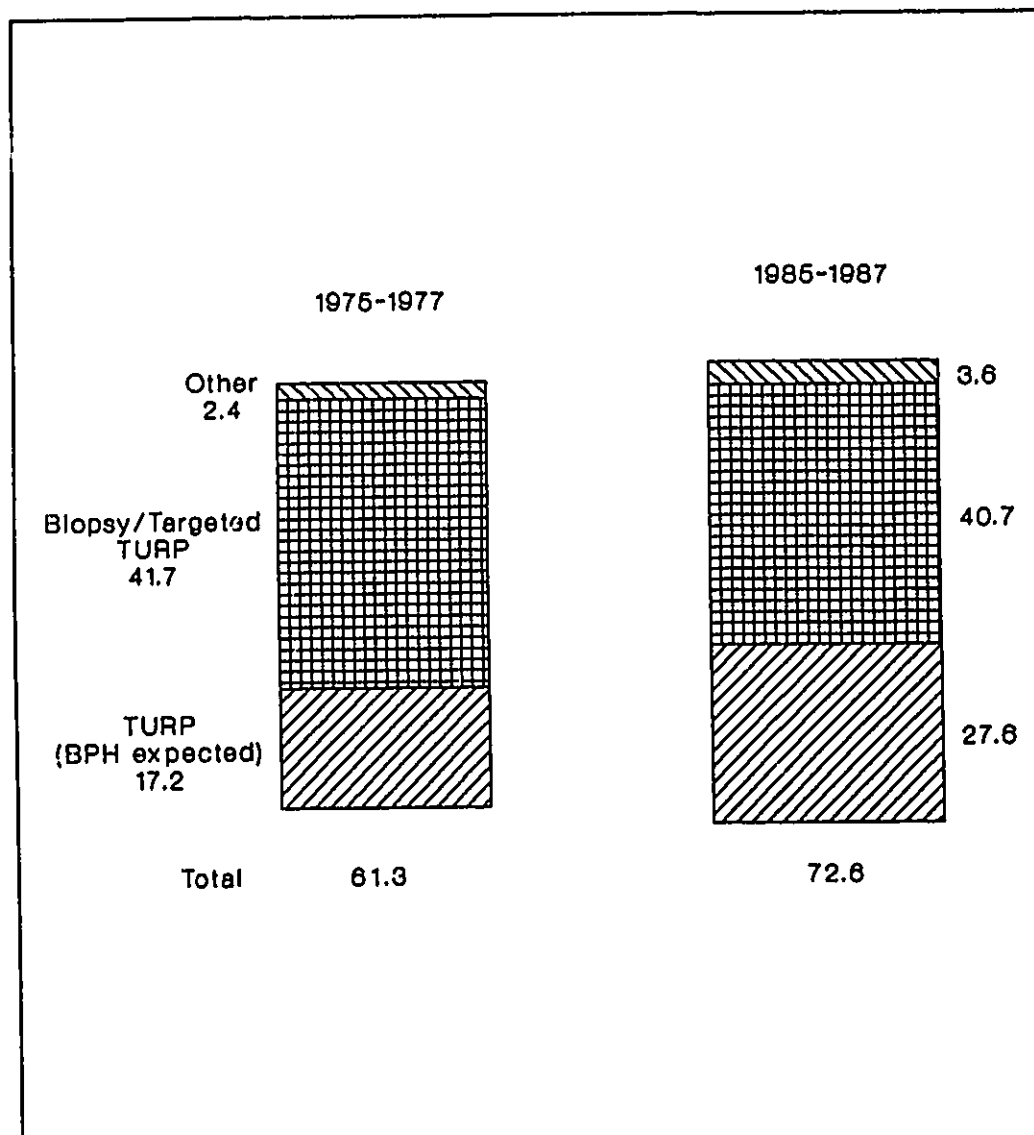


FIGURE 16 Estimated distribution of the procedures used to obtain tissue first for the diagnosis of prostate cancer in residents of Ottawa-Carleton for 1975-7 and 1985-7. Rates are per 100,000, standardised to the 1981 Canadian population.

TABLE 2: Comparison between 1976 and 1986, in cases of BPH, of the means (\pm SE) of the number of slides per patient examined in the laboratory, the mass of prostate tissue per patient submitted to the laboratory, and the number of slides examined per 10 grams of tissue submitted

	1976 (n=115)	1986 (n=132)
SLIDES EXAMINED	2.5 \pm 0.2	4.4 \pm 0.2
MASS OF TISSUE SUBMITTED (g)	17.6 \pm 1.3	17.4 \pm 0.1
SLIDES EXAMINED PER 10g OF TISSUE SUBMITTED	1.7 \pm 0.1	2.9 \pm 0.1

TABLE 3: Comparison between 1976 and 1986/7, in cases of latent prostatic cancer, of the means (\pm SE) of the number of slides per patient examined in the laboratory, the mass of prostate tissue per patient submitted to the laboratory, and the number of slides examined per 10 grams of tissue submitted

	1976 (n=19)	1986/7 (n=34)
SLIDES EXAMINED	2.6 \pm 0.3	4.0 \pm 0.4
MASS OF TISSUE SUBMITTED (g)	15.0 \pm 2.4	13.4 \pm 1.8
SLIDES EXAMINED PER 10g OF TISSUE SUBMITTED	2.3 \pm 0.3	3.8 \pm 0.4

The mean number of slides analyzed by pathologists per 10 grams of prostatic tissue submitted following TURP was 65-70% greater in 1986/7 than in 1976. This observation held both for cases diagnosed as having BPH (70%) and for those diagnosed incidentally as having malignant disease (65%). The increase was due to an increase in the number of slides being prepared in the laboratory, rather than an increase in the amount of tissue being removed by the surgeon. For both groups

ANCOVA performed on the square root transformed number of slides^d, with mass of tissue as a covariate, showed that there was a significant ($p < 0.001$) difference between the two time periods in the number of slides examined after adjusting for the mass of tissue submitted.

In both time periods the cases who had been diagnosed with latent cancer had more slides examined by pathologists per 10 grams of tissue submitted than did those cases who were diagnosed with BPH. In addition, table 4 shows that a significantly increased proportion of men undergoing TURP in 1986 had at least 12 grams of tissue submitted after TURP and at least six slides examined in the pathology laboratory compared to 1976. (It can be estimated that this combination of characteristics of a case will result in approximately 90% of latent cancers being discovered^{76,77}.)

^d The number of slides examined by pathologists has a Poisson distribution. Square root transformation was performed to remstabilize the variance.

TABLE 4: Comparison between 1976 and 1986, of the number of cases with BPH in whom at least 12 grams of tissue were submitted after TURP and at least six slides were examined in the pathology laboratory

	1976 (n=115)	1986 (n=132)
AT LEAST 12 GRAMS OF TISSUE SUBMITTED AND AT LEAST 6 SLIDES EXAMINED	7	30
LESS THAN 12 GRAMS OF TISSUE SUBMITTED OR LESS THAN 6 SLIDES EXAMINED	108	102

p < 0.01

DISCUSSION

Methodological Issues

Several issues require further comment. Some generic problems and technical difficulties associated with undertaking chart review (e.g. missing charts, incomplete data, etc) and obtaining data from national databases (e.g. differing sources of information used by each provincial authority) have already been mentioned.

Other methodological issues which may have limited the conclusions to be drawn from this study include:

Selection bias

There is an inherent selection bias associated with using a hospital population for the sampling frame. However, most cases of prostate cancer are admitted to hospital, at least for initial confirmation of the diagnosis (where the diagnosis is not incidental), and all prostatectomies are performed in hospital. At the Ottawa Civic Hospital Pathology Department there were no specimens of prostate tissue received from out-patients during the two time periods. This was, therefore, not considered to be a significant issue.

"Blinding" the reviewer

The author of this thesis undertook all the chart reviews. It was not possible to be blinded when reviewing the charts, since the mode of storage of charts was

different for the two time periods. To avoid an observation bias only objective information from the charts was used in defining the variable categories into which the patient fell. Furthermore, charts from both periods were reviewed every day, in order to ensure that potential effects of acquiring experience were shared equally across both groups.

Generalisability of the results

The Ottawa Civic Hospital is a 780 bed tertiary care facility, with a referral base of approximately 778,000 residents of Eastern Ontario and Western Quebec. Between 1976 and 1986 the number of adult medical and surgical beds staffed and in operation in the facility fluctuated between 724 beds and 816 beds, but the proportion of beds as a total of all the beds available in Ottawa-Carleton remained almost constant, at 40-42% (Ms. H. McCormack, Ottawa-Carleton Regional District Health Council - Personal communication).

There may have been changes in the underlying population, from which the sample was drawn, in the two time periods. In 1976 there were 252,068 males in Ottawa-Carleton. This number increased to 294,610 in 1986 (Ms. G. Lauris Elkholy, Ontario Ministry of Health - Personal communication). However, the age distributions of men with prostate cancer did not change significantly in the two time periods in either the Ottawa-Carleton population or the sample selected from the Ottawa Civic Hospital, and the two populations were comparable to each other in both time periods. Furthermore, the proportion of cases discharged from the

Ottawa Civic Hospital who were residents of Ottawa-Carleton did not change between the two time periods.

A more sophisticated comparison between the referral populations of the hospital during the two time periods could not be undertaken, because information from which institution-specific referral populations can be derived is not kept by the Ontario Ministry of Health for more than 10 years.

Another concern is the limited number of data points used in the chart review section of this study. It is recognised that interpreting results of what is, essentially, a time-series analysis with two data points should be undertaken with caution.

Absence of data on variables of potential interest

Ideally information relating to risk factor status of individual patients (e.g. race, smoking, diet, sexual history, pesticide use, etc) would have been collected in the chart review component of the study. Unfortunately, because of the nature of clinical records, such information was unavailable for most, or all, cases, and hence the analysis of the data could not take the potential effects of these factors into account. However, since the evidence in the literature linking almost all the proposed risk factors to prostate cancer is weak and controversial, the inability to adjust for these possible confounders was considered not to be a substantive problem from the point of view of interpreting the findings of this study.

Data quality

Population-based registries facilitate the monitoring of incidence and mortality statistics over time and by geographic area. The National databases used in this study are regarded as being of high quality^{2,78,79}. However, the National Hospital Morbidity Statistics Database collates information which is originally collected for administrative purposes rather than research purposes. Thus, although the information is close to 100% complete, the trends in surgical procedures do not take into account the possibility of a single person having more than one TURP. The estimated rates of reoperation following TURP are 10-13%^{13,38}, but this was not taken into account when plotting TURP trends.

As stated previously in this report, the quality of the data from the chart reviews was good, and it is believed that the handling of missing values could not have distorted the general conclusions. The proportion of miscoded cases was very small.

Interpretation of the Findings in this Study

While both incidence and mortality rates from prostate cancer have increased over the past several decades in Canada, incidence rates have increased at a much more rapid rate. This has occurred over a period when there were no major advances in therapy for the disease, and therefore suggests that early detection may, indeed, have accounted for much of the increase in observed incidence rates. It has been suggested previously that increased use of TURPs to treat BPH may have led to an artefactual increase in prostate cancer incidence^{13,37}. The data presented here

show that TURP rates have increased over the time period of this study, as have the rates of total prostatectomies. This increase has been fairly consistent, with a small deviation from the trend associated with a change in procedure classification systems in 1979. By 1987, TURPs represented over 95% of all prostatectomies performed in Canada. This concurs with figures for the United States³⁸, and since the use of other types of prostatectomy is often restricted to patients with unusually large glands or known malignant disease³⁸, TURP rates, rather than total prostatectomy rates, were used in the analysis of a relationship between prostatectomy and incidence rates.

There is an east to west gradient in the pattern of prostate cancer incidence in Canada, which is not mirrored by the mortality rate. Geographical variations in incidence rates may indicate variation in practice patterns², and there is indeed a similar east to west gradient noted in the pattern of TURP rates in Canada, suggesting that practice variation may account for the trends.

Thus national data show evidence, both temporal and spatial, of a direct correlation between prostate cancer incidence rates and TURP rates. The magnitude of the linear correlation between provincial TURP and prostate cancer incidence rates is less than that between the Canadian rates over time. This may be because the linear regression was performed on only 10 data points, leading to an increase in the variance of the estimate, and thus reducing the magnitude of the correlation. Nevertheless, the data show strong positive correlations between the increasing

rates of TURPs and increasing incidence of prostate cancer, suggesting increased case finding. These associations are ecological, however, and therefore cannot be construed as causal. It is plausible, for example, that prostate cancer is the independent variable in the association, driving the rate of TURPs.

Potosky et al, using SEER data from four areas in the United States¹³, found equally strong linear correlations between both total and localized prostate cancer incidence rates and TURP rates over time, and concluded that rising incidence rates are primarily due to increased detection of formerly undiagnosed latent tumours as a result of an increased number of TURPs used to treat BPH. However, that study was purely ecological in nature. No work has previously been undertaken to explore the temporal relationship between the use of TURPs and the discovery of prostate cancer. This thesis contributes the first observations at the level of the individual, rather than the group. The data from the hospital chart review show that an increase in the proportion of cancers *diagnosed incidentally following TURP specifically for suspected BPH* did occur over time (although this increase was not statistically significant), and that this increase can explain much of the increase in observed incidence rate.

The percentage of all prostate carcinomas diagnosed by TURPs in Canada is not known, nor is it known if rates of other methods of diagnosis such as DRE or needle biopsy have increased during the study period. However, data from the United States indicate that over 50% of prostate cancers are diagnosed by TURP⁸⁰.

The data from the Ottawa Civic Hospital show that approximately 40% of cancers were diagnosed by TURP in 1976, a proportion which increased to 49% by 1986.

The chart reviews also revealed that between the mid 1970's and the mid 1980's the increase in observed incidence rates can be attributed to an increase in rates of latent and localised disease. Most of the increase was due to an increase in incidentally discovered disease, with a smaller increase in disease discovered through routine examination. It is conceivable that as more disease is detected earlier in the course of its natural history, the pool of men who develop symptomatic, clinically evident disease shrinks.

The findings showing increased rates of early cancer suggest that improvements in case ascertainment may have contributed to the observed rise in overall incidence. As described in the introductory remarks of this thesis, it is well known that there are latent and active forms of prostatic cancer. When latent cancers are detected incidentally they are recorded as stage A disease, and contribute to the numerator of the incidence rate. An increase in the diagnosis of early stage prostatic tumours will presumably lead to an increase in prostate cancer survival due to lead time bias. In fact, data from Canada^{1,81} and the US⁸² show that prostate cancer survival increased between 1970 and 1980, and Byar⁸² has postulated that a general shift towards earlier diagnosis could account for the observed increase in survival. (It has already been noted that advances in therapy are not likely to have contributed to increased survival rates³³.) The increase in survival over time explains the

described discrepancy between the incidence and mortality rates.

There have been numerous advances in the area of prostate cancer detection in recent years. Immunological markers (e.g. PSA), TRUS probes, and spring biopsy guns have been developed^{31,42,47,83}. The time periods chosen for this study specifically eliminated the potential impact of these influences, as none was in use at the Ottawa Civic Hospital during the study period. Earlier detection could, however, be a function of heightened health awareness and a greater tendency for patients to visit general practitioners (GPs), either for routine examinations or earlier in the natural history of obstructive prostatic symptoms, or to a greater tendency by GPs to perform digital rectal examinations, possibly with a higher index of suspicion for cancer. The apparent shift, seen in the subgroup analyses, to earlier stage disease in cases who were detected following presentation with suspicious signs and symptoms, and in those who were detected at routine examination, suggests that these factors may have contributed to the observed trend, but further studies are required to test these hypotheses. Finally, greater numbers of TURPs, or the subjecting of TURP surgical specimens to an increased level of scrutiny in the pathology laboratory, would contribute to earlier detection.

TURP is known to be the commonest method of obtaining tissue for the diagnosis of prostatic cancer^{69,84}, but, as noted above, it is usually impossible to know whether the diagnosis was a surprise to the physician following surgery for putative BPH, or whether cancer had already been diagnosed or considered. This work shows an

increase over time in the proportion of cancers diagnosed in men who had undergone TURP specifically for BPH. However, the fact that there was not an increase in the absolute numbers of TURPs performed at the Ottawa Civic Hospital in 1986 as compared to 1976 suggests that these findings are not consequent on more specimens reaching the laboratory. Rather, the results indicate that the source of this artefact may be in the pathology laboratory itself.

Although the number of slides required for optimal pathological examination has not been established, there is no doubt that the number of latent cancers discovered is directly proportional to the amount of tissue examined⁷⁰. More slides were analyzed per 10 grams of tissue submitted after TURP in 1986/7 than in 1976, whether the cases were ultimately diagnosed as BPH or as prostatic cancer. This was not consequent on more aggressive surgery (i.e. more tissue being removed at prostatectomy per patient), but rather on an increase in the number of slides made per patient, despite a constant amount of tissue being received in the pathology laboratory. The work reported here is the first to suggest that changes in the handling of prostatectomy specimens in the histopathology laboratory have contributed to greater detection of prostate cancer over time.

Conclusions

Early prostatic cancer is often found as a result of routine screening, or by detecting unsuspected, latent tumour in TURP specimens. The data presented show that earlier detection of disease has been a major contributor to the observed

increase in incidence. This has been due, in large part, to increased detection of carcinoma in putatively benign prostatic lesions following increased scrutiny of prostatectomy specimens in the surgical pathology laboratory. This work is the first to show an association, other than an ecological one, between TURPs and the increased detection of prostate cancer, and the first to assess the source of this increase as being, at least in one institution, the histopathology laboratory. These findings will appear in the peer reviewed literature⁸⁵.

Nevertheless, mortality from prostate cancer has increased over time. This suggests that increased detection alone may not be responsible for the rise in incidence rates. Decreasing mortality from competing risks, such as cardiovascular disease, may explain the increase in mortality¹³, but it remains possible that increasing prostate cancer mortality and incidence rates are due, in part, to increased exposure to unknown etiologic agents.

Recommendations

1. Service planners should recognise that the rising rates of prostate cancer are due, at least in part, to a greater tendency to diagnose early disease which has little impact on prognosis.
2. Assessment of stage-specific survival over time will help to further elucidate the role of early detection in the epidemiology of this important public

health problem. It is suggested that this be a priority for epidemiological research on this subject in the future.

3. Notwithstanding recommendation 1, and in light of the increase in mortality rates from this disease, complacency is not warranted. Aetiological research should remain a priority for epidemiological research in the future.

REFERENCES

- 1) National Cancer Institute of Canada: Canadian Cancer Statistics, 1992. Toronto, Canada, 1992.
- 2) Canadian Council of Cancer Registries, Health and Welfare Canada, Statistics Canada. The making of the Canadian Cancer Registry: Cancer incidence in Canada and its regions, 1969 to 1988. Minister of Supply and Services Canada, 1993.
- 3) Ayiomamitis A. Epidemiology of cancer of the prostate in Canada: 1950-1984. *Brit J Urol* 1987; 60:157-161.
- 4) Ontario Cancer Treatment and Research Foundation. Cancer trends in Ontario. In: Proceedings of the Cancer Epidemiology Seminar, 1990.
- 5) Whelan SL, Parkin DM, Masuyer E. Patterns of cancer in five continents. Lyon: International Agency for Research on Cancer; 1990: Scientific Publication No. 102.
- 6) International Agency for Research on Cancer. Cancer incidence in five continents. Volume V, 1987.
- 7) Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975; 15:617-31.
- 8) Flanders WD. Review: Prostate cancer epidemiology. *Prostate* 1984; 5:621-629.
- 9) Meikle AW, Smith JA. Epidemiology of prostate cancer. *Urologic Clinics of North America* 1990; 17(4):709-18.
- 10) Haenszel W. Cancer mortality among the foreign-born in the United States. *J Natl Cancer Inst* 1961; 26:37-132.
- 11) Staszewski J, Haenszel W. Cancer mortality among the Polish-born in the United States. *J Natl Cancer Inst* 1965; 35:291-7.
- 12) Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst* 1968; 40:43-68.
- 13) Potosky AL, Kessler L, Gridley G, et al. Rise in prostatic cancer incidence associated with increased use of transurethral resection. *J Natl Cancer Inst* 1990; 82(20):1624-28.
- 14) Kolonel LN, Yoshizawa CN, Hankin JH. Diet and prostatic cancer: a case-control study in Hawaii. *Am J Epidemiol* 1988; 127:999-1012.

- 15) Heshmat MY, Kaul L, Kovi J, et al. Nutrition and prostate cancer: a case-control study. *Prostate* 1985; 6:7-17.
- 16) Graham S, Haughey B, Marshall J, et al. Diet in the epidemiology of carcinoma of the prostate gland. *J Natl Cancer Inst* 1983; 70:687-92.
- 17) Elghany NA, Schumacher MC, Slattery ML, et al. Occupation, cadmium exposure, and prostate cancer. *Epidemiology* 1990; 1:107-15.
- 18) Mettlin C, Natarajan N, Huben R. Vasectomy and prostate cancer risk. *Am J Epidemiol* 1990; 132:1056.
- 19) Honda GD, Bernstein L, Ross RK, et al. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 1988; 57:326-331.
- 20) Hayes RB, Pottern LM, Greenberg R, et al. Vasectomy and prostate cancer in US blacks and whites. *Am J Epidemiol* 1993; 137(3):263-269.
- 21) DerSimonian R, Clemens J, Spirtas R, et al. Vasectomy and prostate cancer risk: methodological review of the evidence. *J Clin Epidemiol* 1993; 46(2):163-172.
- 22) Blair A, Zahm SH. Cancer among farmers. *Occup Med* 1991; 6:335-354
- 23) Morrison H, Savitz D, Semenciw R, et al. Farming and prostate cancer mortality. *Am J Epidemiol* 1993; 137(3):270-280.
- 24) Nomura AMY, Kolonel LN. Prostate cancer: a current perspective. *Epidemiol Rev* 1991; 13:200-207.
- 25) Ghadirian P, Cadotte M, Lacroix A, et al. Family aggregation of cancer of the prostate in Quebec: the tip of the iceberg. *Prostate* 1991; 19:43-52.
- 26) Fincham SM, Hill GB, Hanson J, et al. Epidemiology of prostatic cancer: a case-control study. *Prostate* 1990; 17:189-206.
- 27) Steinberg GD, Carter BS, Beaty TH, et al. Family history and the risk of prostate cancer. *Prostate* 1990; 17:337-47.
- 28) Spitz MR, Currier RD, Fueger JJ, et al. Familial pattern of prostate cancer: a case-control analysis. *J Urology* 1991; 146:1305-7.
- 29) Mettlin C, Natarajan N. End results for urologic cancers. *Cancer* 1987; 60:474-479.
- 30) Carter HB, Coffey DS. The prostate: an increasing medical problem. *Prostate* 1990; 16:39-48.
- 31) Gittes RF. Carcinoma of the Prostate. *N Engl J Med* 1991; 324(4):236-45.

- 32) Sheldon CA, Williams RD, Fraley EE. Incidental carcinoma of the prostate: a review of the literature and critical reappraisal of classification. *J Virol* 1980; 124:626-31.
- 33) Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1991 update: 3. Secondary prevention of prostate cancer. *Can Med Assoc J* 1991; 145:413-428.
- 34) Epstein JI, Paull G, Eggleston JC, et al. Prognosis of untreated stage A1 prostatic carcinoma: a study of 94 cases with extended follow up. *J Urol* 1986; 136:837-839.
- 35) Anonymous. Keeping tabs on prostate cancer. University of Toronto Faculty of Medicine, *Health News* 1991; 9(5):7-9.
- 36) Schroder FH. Prostate cancer: to screen or not to screen? *Br Med J* 1993; 306:407-408.
- 37) Severson RK. Have transurethral resections contributed to the increasing incidence of prostatic cancer? *J Natl Cancer Inst* 1990; 82(20):1597-98.
- 38) Roos NP, Wennberg JE, Malenka DJ, et al. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. *N Engl J Med* 1989; 320(17):1120-24.
- 39) Guileyardo JM, Johnson WD, Welsh RA, et al. Prevalence of latent prostate carcinoma in two U.S. populations. *J Natl Cancer Inst* 1980; 65:311-6.
- 40) Dunn JE. Cancer epidemiology in populations of the United States - with emphasis on Hawaii and California, and Japan. *Cancer Res* 1975; 35:3240-3245.
- 41) Breslow N, Chan CW, Dhom G, et al. Latent carcinoma of the prostate at autopsy in seven areas. *Int J Cancer* 1977; 20:680-688.
- 42) Dohm G. Epidemiologic aspects of latent and clinically manifest carcinoma of the prostate. *J Cancer Res Clin Oncol* 1983; 106:210-18.
- 43) Donn AS, Muir CS. Prostatic cancer: some epidemiological features. *Bull Cancer (Paris)* 1985; 72:381-90.
- 44) Montie JE, Wood DP Jr, Pontes JE, et al. Adenocarcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. *Cancer* 1989; 63:381-5.
- 45) Chodak GW, Keller P, Schoenberg HW. Assessment of screening for prostate cancer using digital rectal examination. *J Urol* 1989; 141:1136-8.
- 46) Stamy TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987; 317:909-16.

- 47) Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991; 324:1156-61.
- 48) Cooner WH, Mosley BR, Rutherford CL, et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol* 1990; 143:1146-1154.
- 49) Thompson IM. Carcinoma of the prostate: Changing incidence associated with annual urologic screening. *Southern Med J* 1989; 82(3):335-337.
- 50) Chodak GW, Schoenberg HW. Early detection of prostate cancer by routine screening. *JAMA* 1984; 252(23):3261-3264.
- 51) Miller AB, Chamberlain J, Day NE, et al. Report on a workshop of the UICC project on the evaluation of screening for cancer. *Int J Cancer* 1990; 46:761-769.
- 52) Canadian Task Force on the Periodic Health Examination. The periodic health examination. *Can Med Assoc J* 1979; 121:1193-1254.
- 53) US Preventive Services Task Force: Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions. Williams & Wilkins, Baltimore 1989:63-65.
- 54) Gerber GS, Thompson IM, Thisted R, et al. Disease-specific survival following routine prostate cancer screening by digital rectal examination. *JAMA* 1993; 269(1):61-64.
- 55) Wigle DT, Mao Y, Wong T, et al: Economic burden of illness in Canada, 1986. *Chronic Diseases in Canada* 1991; 12(3 Suppl).
- 56) Gaudette LA. The Canadian National Cancer Incidence Reporting System. *Chronic Diseases in Canada* 1986; 6(4):73-76.
- 57) Statistics Canada. Causes of death. Annual. Catalogue 84-203. Ottawa, Supply and Services Canada.
- 58) Health and Welfare Canada and Statistics Canada. Mortality atlas of Canada Volume 4: General mortality patterns and recent trends. 1991. Catalogue H-49-6/4-1990. Ottawa, Supply and Services Canada.
- 59) Statistics Canada. Cancer in Canada. Annual. Catalogue number 82-207. Ottawa, Supply and Services Canada.
- 60) Statistics Canada. Surgical procedures and treatments. Annual. Catalogue 82-208. Ottawa, Supply and Services Canada.
- 61) Statistics Canada. Hospital morbidity. Annual. Catalogue 82-206. Ottawa, Supply and Services Canada.

- 62) National Centre for Health Statistics: International classification of diseases, 8th revision: Adapted for use in the United States. Washington, DC: US Gov't Print Office, 1967.
- 63) National Centre for Health Statistics: International classification of diseases, 9th revision: Clinical modification. Washington, DC. US Gov't Print Office, 1980.
- 64) Statistics Canada. Intercensal annual estimates of population by sex and age for Canada, provinces and territories (occasional). 1966-71, 1971-76, 1976-81, 1981-1986. Catalogue 91-518. Ottawa, Supply and Services Canada.
- 65) Statistics Canada. Postcensal annual estimates of population by marital status, age, sex and components of growth for Canada, provinces and territories (occasional). 1987, 1988. Catalogue 91-210. Ottawa, Supply and Services Canada.
- 66) Statistics Canada. 1981 Census of Canada. Ottawa, 1987. Catalogue 93-101. Ottawa, Supply and Services Canada.
- 67) Statistics Canada Health Division. Canadian classification of diagnostic, therapeutic and surgical procedures. 1st edition 1978.
- 68) Kirkwood BR. Essentials of Medical Statistics. Blackwell Scientific Publications, Oxford, 1988.
- 69) Murphy GP, Natarajan N, Pontes JE, et al. The national survey of prostate cancer in the United States by the American College of Surgeons. J Urol 1982; 127:928-934.
- 70) Murphy WM. Urological Pathology. Philadelphia: WB Saunders Company, 1989.
- 71) Statistics Canada (Geography Division). Postal Code Conversion File: Summary documentation. Ottawa, 1991. Statistics Canada.
- 72) Statistics Canada. Census of Canada 1986 Reference Dictionary. Ottawa, 1987. Catalogue 99-101E. Supply and Services Canada.
- 73) Committee on Nomenclature and Classification of Disease: Systematized Nomenclature of Pathology, 2nd edition. College of American Pathologists, 1969.
- 74) Committee on Nomenclature and Classification of Disease: SNOMED; Systematized Nomenclature of Medicine, 2nd edition. College of American Pathologists, 1982.
- 75) Streiner DL. Sample size and power in psychiatric research. Can J Psychiatry 1990; 35(7):616-620.
- 76) Moore GH, Lawshe B, Murphy J. Diagnosis of adenocarcinoma in transurethral resectates of the prostate gland. Am J Surg Pathol 1986; 10(3):165-69.

- 77) Murphy WM, Dean PJ, Brasfield JA, et al. Incidental carcinoma of the prostate. How much sampling is adequate? *Am J Surg Pathol* 1986; 10(3):170-174.
- 78) Langlet ER, Gaudette LA. Data quality assessment for the National Cancer Incidence Reporting System, Canada and the provinces 1970-1984 Technical Report. Canadian Centre for Health Information, Statistics Canada, Ottawa, October 1989.
- 79) Reynolds DL, Nguyen VC, Clarke EA. Reliability of cancer mortality statistics in Ontario: A comparison of incident and death diagnoses, 1979-1983. *Can J Public Health* 1991; 82(2):120-126.
- 80) Schmidt JD, Mettlin CJ, Natarajan N, et al. Trends in patterns of care for prostatic cancer, 1974-1983: results of surveys by the American College of Surgeons. *J Urol* 1986; 136:416-21.
- 81) Mao Y, Robson D, Semenciw RM, et al. Long term survival rates among patients with cancer in Saskatchewan. *Can J Publ Health* 1991; 82:413-20.
- 82) Byar DP. Incidence, mortality and survival statistics for prostatic cancer. In: *Current Concepts and Approaches to the Study of Prostate Cancer*. (Coffey DS, Bruchovsky N, Gardner WA, et al, eds.) New York: Liss, 1987, pp 785-796.
- 83) Murphy GP. The current and potential status of screening for prostatic cancer in asymptomatic populations. *Prog Clin Biol Res* 1989; 303:19-25.
- 84) Humphrey P, Vollmer RT. The ratio of prostate chips with cancer: A new measure of tumor extent and its relationship to grade and prognosis. *Hum Pathol* 1988; 19:411-418.
- 85) Levy IG, Gibbons L, Collins JP, Mao Y and Perkins DG. Prostate cancer trends in Canada: rising incidence or increased detection? *Can Med Assoc J*. In press.

APPENDICES**APPENDIX A - Information sources used by the provincial agencies that supply information to the NCIRS²**

	CANCER TREATMENT AGENCY RECORDS	PATHOLOGY LABORATORY REPORTS	HAEMATOLOGY LABORATORY REPORTS	DEATH CERTIFICATES	HOSPITAL SEPARATION RECORDS	AUTOPSY REPORTS	MEDICARE CLAIMS
BRITISH COLUMBIA	*	*	*	*	*	*	
ALBERTA	*	*	*	*	*	*	
SASKATCHEWAN	*	*	*	*	*	*	*
MANITOBA	*	*	*	*	*	*	*
ONTARIO	*	*	*	*	*	*	
QUEBEC					*		
NEW BRUNSWICK	*	*	*	*		*	
NOVA SCOTIA	*	*		*	*	*	
PRINCE EDWARD ISLAND	*	*	*	*		*	
NEWFOUNDLAND	*	*	*	*	*	*	
YUKON	*	*					
NORTH WEST TERRITORIES	*			*	*		

APPENDIX B - The Canadian male population, 1981⁶⁶

AGE GROUP (Years)	NUMBER (%)
Under 1	186,320 (1.5)
1-4	728,130 (6.0)
5-9	911,940 (7.6)
10-14	984,740 (8.2)
15-19	1,182,015 (9.8)
20-24	1,174,295 (9.7)
25-29	1,084,415 (9.0)
30-34	1,021,480 (8.5)
35-39	822,300 (6.8)
40-44	674,665 (5.6)
45-49	634,705 (5.3)
50-54	621,655 (5.2)
55-59	568,385 (4.7)
60-64	462,385 (3.8)
65-69	390,580 (3.2)
70-74	281,230 (2.3)
75-79	180,480 (1.5)
80-84	94,935 (0.8)
85-89	44,020 (0.4)
> 90	19,610 (0.2)
TOTAL	12,068,290 (100)

APPENDIX C - Codings used in the various coding systems referred to in this thesis

Code

Prostate cancer

**International Classification of Diseases (ICD)
Versions 8⁶² and 9⁶³**

Carcinoma of the Prostate: 185

Surgical/diagnostic procedures

ICD Procedures (Version 8⁶²)

Transurethral prostatectomy: 58.2
Other prostatectomies (e.g. suprapubic): 58.0
58.1
58.3

**Canadian Classification of Diagnostic,
Therapeutic and Surgical Procedures (CCDTSP)⁶⁷**

Transurethral prostatectomy: 72.1
Other prostatectomies (e.g. suprapubic): 72.0
72.2-5

Histopathological diagnoses

**Systematized Nomenclature of Pathology
(SNOP system)⁷³**

Benign Prostatic Hypertrophy
Topographical code: 77
Morphological code: 7300

**Systematized Nomenclature of Medicine
(SNOMED system)⁷⁴**

Benign Prostatic Hypertrophy
Topographical code: 77
Morphological codes: 72000
72030
72120
72400
72420
72460

APPENDIX D - Sample size calculation for the analysis of changes in clinical stage and process leading to the diagnosis

The formula for the comparison of two proportions is:

$$n \text{ (in each group)} = \frac{[Z_{\alpha/2} \sqrt{(p_1q_1 + p_2q_2)} + Z_{\beta} \sqrt{2PQ}]^2}{[p_2 - p_1]^2}$$

where $P = (p_1 + p_2)/2$

This table shows the sample size required to detect, with 80% power, a 20% change in early stage disease, as a function of the initial proportion of early stage disease ($\alpha=0.05$):

% Stage A or Stage B in 1976	Estimated sample size for 80% power
10	62
20	82
30	93
40	97
50	93

APPENDIX E - Data sheet used for chart reviews

STUDY I.D..... YEAR.....

RESIDENCE (POSTAL CODE).....

YEAR OF DIAGNOSIS.....

AGE AT DIAGNOSIS.....

PLACE OF DIAGNOSIS: Civic Hospital.....
Other.....

CLINICAL STAGE.....

SYMPTOMS: Yes (specify).....
No.....
Unknown.....

ORIGINAL REASON FOR SUSPICION:
Not suspected (followed TURP).....
Routine DRE-suspicious lesion.....
Symptoms-DRE-suspicious lesion.....
Other.....

PROCEDURES: Targeted biopsy only.....
Targeted TURP (Ca suspected).....
Incidental finding at TURP
(BPH suspected).....
Other (Specify).....

HISTOLOGIC TYPE (Adenoca is the default).....

PATHOLOGICAL INFORMATION: Grams submitted.....
(only for TURPs) Cassettes made.....
Cassettes per gram.....

APPENDIX F - Test of the assumption that the proportion of variables of interest (e.g. circumstances preceding diagnosis) is the same in each age category

1976

AGE CATEGORY (Yrs)	SYMPTOMS EXPECT BPH	ROUTINELY DETECTED	SYMPTOMS EXPECT CA	Total
<70	10	7	12	29
70-79	5	8	16	29
>79	5	4	4	13
Total	20	19	32	71

Chi square = 3.68
 Degrees of freedom = 4
 p value = 0.45944563

1986/7

AGE CATEGORY (Yrs)	SYMPTOMS EXPECT BPH	ROUTINELY DETECTED	SYMPTOMS EXPECT CA	Total
<70	13	7	9	29
70-79	16	19	16	51
>79	10	2	7	19
Total	39	28	32	99

Chi square = 5.79
 Degrees of freedom = 4
 p value = 0.21534868

APPENDIX G - Canada Post's Forward Sorting Areas corresponding to Ottawa-Carleton boundaries^c

The Forward Sorting Area is defined by the first three spaces of the postal code. The following are those which are contained within the perimeter of the Ottawa-Carleton census division:

K0A
K1B
K1C
K1E
K1G
K1H
K1J
K1K
K1L
K1M
K1N
K1P
K1R
K1S
K1T
K1V

K1W
K1Y
K1Z
K2A
K2B
K2C
K2E
K2G
K2H
K2J
K2K
K2L
K2M
K2P
K4A
K4B

^c Source: Mr. Russell Wilkins, Canadian Centre for Health Information, Statistics Canada

APPENDIX H - List of abbreviations used in this thesis

ANCOVA:	Analysis of Covariance
BPH:	Benign Prostatic Hypertrophy
Ca:	Cancer
CCDTSP:	Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures
CMDB:	Canadian Mortality Database
DRE:	Digital Rectal Examination
FSA:	Forward Sorting Area
GP:	General Practitioner
HMRI:	Hospital Medical Records Institute
ICD:	International Classification of Diseases
NCIRS:	National Cancer Incidence Reporting System
O-C:	Ottawa-Carleton
OCH:	Ottawa Civic Hospital
PSA:	Prostate Specific Antigen
SNOMED:	Systematized Nomenclature of Medicine
SNOP:	Systematized Nomenclature of Pathology
TRUS:	Transrectal Ultrasound
TURP:	Transurethral Prostatectomy