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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

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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 cancer\textsuperscript{1}. It is the commonest site of new cancers in men aged 75 years and over\textsuperscript{2}. Figure 1 shows the breakdown of cancer incidence in males, over the period of 1984-1988\textsuperscript{2}.

Over the last two decades reported incidence and mortality rates due to prostate cancer have steadily increased\textsuperscript{3}, and in parts of western Canada the number of new cases is now estimated to exceed that of lung cancer\textsuperscript{1}. It has been projected that by 1995 this situation will exist in Canada’s most populous province, Ontario\textsuperscript{4}. The Canadian rate is already among the three highest international rates\textsuperscript{5}, and the lifetime probability of a Canadian male developing prostate cancer is now 8.75\%\textsuperscript{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)\textsuperscript{1}. 

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

*Excludes non-melanotic cutaneous cancer
** Non-Hodgkins Lymphoma
Source: Reference 2

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 Asia[6-3]. 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 Californians\textsuperscript{9}. Rising rates are found among various groups migrating from low to high risk geographical areas\textsuperscript{10-12}. These observations, and others showing the presence of birth cohort effects in various populations\textsuperscript{13}, suggest an aetiological role for modifiable environmental factors. Several factors have been proposed as possible risk factors. Dietary fat and vitamin A\textsuperscript{14-16}, and cadmium exposure through cigarette smoke or occupation\textsuperscript{17} 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 performed\textsuperscript{9}, and recently much debate has centred around the role of vasectomy as a risk factor\textsuperscript{18-21}. Other reports have linked the occupation of farming to the disease\textsuperscript{22,23}, possibly related to exposure to pesticides\textsuperscript{23}. However, epidemiological studies have failed to determine, conclusively, a causal agent\textsuperscript{9,19,24}, and only increasing age and a positive family history\textsuperscript{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\textsuperscript{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 aggressive\textsuperscript{31-36}, 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\textsuperscript{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 prostatectomy. The commonest form of prostatectomy performed in North America is the transurethral prostatectomy (TURP), representing more than 95% of prostatectomies performed in certain areas.

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.

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 1986\textsuperscript{55}. More than $7 billion dollars (almost 80\%) of this amount was due to the indirect costs of premature mortality\textsuperscript{55}. Prostate cancer is responsible for 3.5\% of all potential years of life lost due to cancer\textsuperscript{1}, 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 (CMDB) 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 covered\(^2\,^5\,^6\). 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 1921\(^{57}\). The CMDB is a computer file of the records of death events since 1950\(^{58}\).

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 information\(^{59}\), and publishes various morbidity reports,
including one relating to surgical procedures\textsuperscript{60}.

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 comparisons\textsuperscript{59}. However, less than two percent of all hospital separations involve patients who are not residents of the reporting province\textsuperscript{61}. 
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 8 for 1969 and 9 for 1979) 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 years.

**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 8\textsuperscript{62}) until 1978, and according to the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures codes\textsuperscript{67} from 1979 (see Appendix C for the relevant codes). Population data were again extracted from Statistics Canada census publications\textsuperscript{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 proportions\(^6^8\). \(\alpha\) was set at 0.05.

Previous work\(^6^9\) 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
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 system, 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 File\textsuperscript{71}, 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)\textsuperscript{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\textsuperscript{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)\textsuperscript{73} for 1976, and the SNOMED system (Systematized Nomenclature of Medicine)\textsuperscript{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.

\textsuperscript{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\(^b\). 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. \( \alpha \) 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:

\[
n = \frac{2\sigma^2(Z_{1-\alpha} + Z_{1-\beta})^2}{\delta^2} \]

where \( \sigma \) = the standard deviation, and \( \mu \) = 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% (r²) 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)

*per 100,000, using 1981 Canadian population as standard
FIGURE 5 Age-standardised prostate cancer incidence and 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 3 (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 prostatic 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 $\alpha$ level of 0.05$^{75}$.

---

The formula for the power calculation is:

$$Z_a = \frac{\sqrt{N}(p_1-p_2)/2}{\sqrt{PQ}} - Z_\alpha$$

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 (ROUTINELEY DETECTED), and following a priori suspicion (SYMPTOMS EXPECT CA)

<table>
<thead>
<tr>
<th></th>
<th>ROUTINELY DETECTED</th>
<th>SYMPTOMS EXPECT CA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1976 (n=18)</td>
<td>1986/7 (n=27)</td>
</tr>
<tr>
<td>LOCALISED DISEASE</td>
<td>67% (n=12)</td>
<td>81% (n=22)</td>
</tr>
<tr>
<td>INVASIVE DISEASE</td>
<td>33% (n=6)</td>
<td>19% (n=5)</td>
</tr>
</tbody>
</table>
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 (±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

<table>
<thead>
<tr>
<th></th>
<th>1976 (n=115)</th>
<th>1986 (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIDES EXAMINED</td>
<td>2.5±0.2</td>
<td>4.4±0.2</td>
</tr>
<tr>
<td>MASS OF TISSUE SUBMITTED (g)</td>
<td>17.6±1.3</td>
<td>17.4±0.1</td>
</tr>
<tr>
<td>SLIDES EXAMINED PER 10g OF TISSUE SUBMITTED</td>
<td>1.7±0.1</td>
<td>2.9±0.1</td>
</tr>
</tbody>
</table>
TABLE 3: Comparison between 1976 and 1986/7, in cases of latent prostatic cancer, of the means (±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

<table>
<thead>
<tr>
<th></th>
<th>1976 (n=19)</th>
<th>1986/7 (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIDES EXAMINED</td>
<td>2.6±0.3</td>
<td>4.0±0.4</td>
</tr>
<tr>
<td>MASS OF TISSUE</td>
<td>15.0±2.4</td>
<td>13.4±1.8</td>
</tr>
<tr>
<td>SUBMITTED (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLIDES EXAMINED</td>
<td>2.3±0.3</td>
<td>3.8±0.4</td>
</tr>
<tr>
<td>PER 10g OF TISSUE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBMITTED</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\textsuperscript{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\textsuperscript{76,77}.)

\textsuperscript{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

<table>
<thead>
<tr>
<th></th>
<th>1976 (n=115)</th>
<th>1986 (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT LEAST 12 GRAMS OF TISSUE SUBMITTED AND AT LEAST 6 SLIDES EXAMINED</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>LESS THAN 12 GRAMS OF TISSUE SUBMITTED OR LESS THAN 6 SLIDES EXAMINED</td>
<td>108</td>
<td>102</td>
</tr>
</tbody>
</table>

\[ p < 0.01 \]
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 Elkady,
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\textsuperscript{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\%\textsuperscript{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.

\textit{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\textsuperscript{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 States\textsuperscript{38}, and since the use of other types of prostatectomy is often restricted to patients with unusually large glands or known malignant disease\textsuperscript{38}, 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 patterns\textsuperscript{2}, 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 States$^{13}$, found equally strong linear correlations between 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 TURP$^{80}$. 
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\textsuperscript{1,81} and the US\textsuperscript{82} show that prostate cancer survival increased between 1970 and 1980, and Byar\textsuperscript{82} 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 rates\textsuperscript{33}. ) 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\textsuperscript{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\textsuperscript{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 examined. 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 literature.  

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 mortality, 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


APPENDICES

APPENDIX A - Information sources used by the provincial agencies that supply information to the NCIRS$^2$

<table>
<thead>
<tr>
<th>Source</th>
<th>Cancer Treatment Agency Records</th>
<th>Pathology Laboratory Reports</th>
<th>Haematology Laboratory Reports</th>
<th>Death Certificates</th>
<th>Hospital Separation Records</th>
<th>Autopsy Reports</th>
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</table>
APPENDIX C - Codings used in the various coding systems referred to in this thesis

Prostate cancer

International Classification of Diseases (ICD)
Versions 8\textsuperscript{a} and 9\textsuperscript{a}

Carcinoma of the Prostate: 185

Surgical/diagnostic procedures

ICD Procedures (Version 8\textsuperscript{a})

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

Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCDTSP)\textsuperscript{b}

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

Histopathological diagnoses

Systematized Nomenclature of Pathology (SNOP system)\textsuperscript{c}

Benign Prostatic Hypertrophy
Topographical code: 77
Morphological code: 7300

Systematized Nomenclature of Medicine (SNOMED system)\textsuperscript{c}

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

\textsuperscript{a} World Health Organization, 1980
\textsuperscript{b} Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures, 1989
\textsuperscript{c} Health, Education, and Welfare, 1978
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:

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

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 (\( \alpha=0.05 \)):

<table>
<thead>
<tr>
<th>% Stage A or Stage B in 1976</th>
<th>Estimated sample size for 80% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>62</td>
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<tr>
<td>20</td>
<td>82</td>
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<td>40</td>
<td>97</td>
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<tr>
<td>50</td>
<td>93</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>AGE CATEGORY (Yrs)</th>
<th>SYMPTOMS EXPECT BPH</th>
<th>ROUTINELY DETECTED</th>
<th>SYMPTOMS EXPECT CA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>10</td>
<td>7</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>70-79</td>
<td>5</td>
<td>8</td>
<td>16</td>
<td>20</td>
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<tr>
<td>&gt;79</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>13</td>
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<tr>
<td>Total</td>
<td>20</td>
<td>19</td>
<td>32</td>
<td>71</td>
</tr>
</tbody>
</table>

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

1986/7

<table>
<thead>
<tr>
<th>AGE CATEGORY (Yrs)</th>
<th>SYMPTOMS EXPECT BPH</th>
<th>ROUTINELY DETECTED</th>
<th>SYMPTOMS EXPECT CA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>13</td>
<td>7</td>
<td>9</td>
<td>29</td>
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<tr>
<td>70-79</td>
<td>16</td>
<td>19</td>
<td>16</td>
<td>51</td>
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<tr>
<td>&gt;79</td>
<td>10</td>
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<td>19</td>
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<tr>
<td>Total</td>
<td>39</td>
<td>28</td>
<td>32</td>
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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

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        K1W
K1B        K1Y
K1C        K1Z
K1E        K2A
K1G        K2B
K1H        K2C
K1J        K2E
K1K        K2G
K1L        K2H
K1M        K2J
K1N        K2K
K1P        K2L
K1R        K2M
K1S        K2P
K1T        K4A
K1V        K4B

* 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