ESTIMATION OF ARTEFACTUAL AND TRUE COMPONENTS OF THE TREND IN PROSTATE CANCER INCIDENCE IN SCOTLAND 1982 - 1990

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Originality Statement

I declare that the contents of this thesis represent my own work; contributions from others have always been explicitly acknowledged.

Signature

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ABSTRACT

Prostate cancer is becoming an increasingly important health problem in Scotland. Its reported incidence increased substantially over the past two decades. Mortality rate also increased but less rapidly than incidence. The disease is the third most commonly registered cancer in males, following lung and large bowel cancers. It is also the second cause of cancer mortality, after lung cancer. Concerns have been raised whether this trend is genuine. A true increase in the risk of PCa cannot be excluded, but artefactual increase has been widely suggested with some evidence for the artefact caused by increased detection of incidental cancer have been reported from the USA.

The aim of the study is to describe the incidence trend in Scotland between 1971 and 1990 and to estimate the artefactual increases due to ageing, improved reporting and increased detection of TURP-detected incidental cases, and the true component in the overall trend.

Methods:

1. Secondary analysis of routine incidence and mortality data with age-specific and age-adjusted rates described.

2. Trend in completeness of Scottish Cancer Registry (SCR) for PCa between 1982 and 1990 was estimated using capture-recapture method to estimate cases unknown to two sources (Scottish Cancer Registry, Scottish Hospital Discharge SMR1).

3. Probability of a case being incidental was determined from a case-note review for 172 selected cases from Lothian. This probability was related to SCR and SMR1

routine data and extrapolated to the Scottish figures of PCa registrations between 1982 and 1990 so that trend in TURP-detected incidental and clinical cases could be estimated.

4. From these, contribution of improvement in completeness, increased incidental cases and ageing to the overall trend was estimated.

Results

More than 90% of cases with an SMR1 for PCa were reported to SCR at the end compared to 86% at the beginning of the study. Clinical PCa constituted majority of all registered cases, but incidental incidence rate increased dramatically (70%) as opposed to 5.7% increase in the clinical PCa incidence. Analysis of the trend shows that out of (540) total increase in registrations between 1982-84 and 1988-90, 24.3% (131 cases) could be explained by improvement in reporting, 34% (184 cases) due to increased detection of incidental cases, 35% (190 cases) due to ageing and 6.5% (35 cases) remain to be explained and may be due to untested components or a genuine increase.

Discussion

More than half of the increase in incidence of PCa is artefactual which is not surprising given the dramatic rise in TURP and the plausibility of improved reporting. The clinical disease also increased, though much slower, reflecting perhaps a real increase in prevalence of risk factors. While the artefactual part is reassuring from public health point of view, for policy makers and finance managers it is a case for arguing against the relative importance of PCa. This, however, has to be considered in the light of similar artefacts in other cancers and some other diseases. The actual increase is present indicating that the disease is to be taken seriously and ways of reducing its morbidity and consequent fatality need to be explored.

GLOSSARY OF ABBREVIATIONS AND DEFINITIONS

DCO: Cancer cases in which death certificate is the only source of notification or ascertainment.

DRE: Digital Rectal Examination

ISD: Information and Statistics Division of the National Health Service in Scotland.

PCa: Prostate Cancer

PIN: Prostatic Intraepithelial Neoplasia

PRR: Proportional Registration Ratio

PSA: prostate specific antigen serum test.

PSU: Primary Site Unknown

SCR: Scottish Cancer Registry

SMR1: Scottish Morbidity Record (1) which is a hospital discharge summary form used to notify the ISD of any hospital admission except those for psychological or gynaecological and obstetric problems.

SMR6: Scottish Morbidity Record for notification of newly diagnosed cancer cases. It is the cancer registry notification.

TRUS: Transrectal Ultrasound

TURP: Transurethral resection of the prostate.

UnK: Unknown age.

Relative completeness of PCa registration:

Is the completeness of cancer registry for PCa cases on the SMR-1 scheme and is equal to the percentage of cases on SMR-1 data scheme that have consistent matches in the SCR records. This is calculated overall and by year of diagnosis, age-group and region.

Estimated completeness of PCa registration:

Is the percentage of the total number of PCa cases estimated by capture-recapture method that have been registered with the SCR.

Truncated rate:

Derived by restricting both the numerator and the population denominator of the rate to specific age-groups of interest with the aim of better assessment of the real risk of the disease. The truncated incidence rate in this thesis is restricted to the age of 55-79.

Incidental prostate cancer case:

one which was diagnosed as an incidental finding of an operation for benign disease (see page 113).

Latent prostate cancer case:

one which is diagnosed at autopsy but was unsuspected during the patient's life time (see page 12)

CHAPTER I

INTRODUCTION

Prostate cancer (PCa) is a disease of elderly. It rarely occurs before fifty years of age and increases sharply after that (Mandel and Schuman 1980).

The disease is becoming an increasingly significant health problem world-wide. Its incidence has increased and is expected to continue to do so through the next century (Boyle 1997). In the United States (USA) incidence and mortality rates have been rising over the last three decades (Devesa et al 1995) and in 1991 the incidence superseded that for lung cancer, becoming the first most commonly reported malignancy among the American men (Boring et al 1991). Similar rising trends have taken place in many other countries (Coleman et al 1993).

Such growing importance of the disease was addressed by researchers and scientists who believe that these trends for PCa are more artefactual than real, being due to population ageing, improved registration and the increase in the number of incidentally-diagnosed prostatic cancers (Doll 1991; Whitmore 1994; Alexander and Boyle 1995).

Ageing of the population is a common demographic characteristic of most countries (Alexander and Boyle 1995), and men are now more likely to live to an age when the risk of developing PCa and the chance of being detected with the disease are high.

Partially, incidence trends reflect improvement of cancer registration caused by progressive improvement in the readiness of physicians to collaborate with the registry by reporting any cases they diagnose (Doll and Peto 1981). Registration can also be

affected by the improvement in the quality of diagnostic information and the consequent improvement in the precision of site coding (Esteve et al 1994).

Between 10 and 21 per cent of transurethral resection of the prostate (TURP) operations performed for treating benign prostatic hypertrophy (BPH) have been associated with detection of clinically unsuspected prostatic carcinoma (Sheldon et al 1980; Denton et al 1965). Therefore, increased use of these operations would be expected to result in increasing trend in the number of these unsuspected cases. Evidence of this contribution by TURP to PCa incidence trend has been reported from the USA (Potosky et al 1990), and the fact that many of the carcinomas detected this way might remain latent and not progress to clinical disease (Catalona and Scott 1978) means that this contribution is mostly artefactual.

Screening for PCa using the prostate specific antigen (PSA) test resulted in increased diagnosis of cases and influenced the overall trend of the disease in the USA during the late eighties (Potosky et al 1995). This effect is likely to be partially artefactual due to increased detection of cases that would not be recognised if screening was not done (Muir et al 1994).

Despite their belief that the international trends in reported incidence are largely artefactual, researchers could not rule out the possibility of a true increase in the risk of the disease (Coleman et al 1993). The change in dietary habits in Japan toward western habits (Kagawa 1978) and the increase in the rate of large latent cancers at autopsy there (Yatani et al 1988) may indirectly indicate a genuine change in risk in Japan. Direct evidence of the real increase in risk follows from evidence of an identified risk factor increasing with time; however, despite the compelling evidence of the role of the environment, the aetiology of prostate cancer is still obscure apart from some

consistent findings on its relation with high intake of dietary fat (Boyle et al 1995; Nomura and Kolonel 1991). A trend for clinically-diagnosed cases alone may provide a surrogate measure for the true component of the trend.

Scotland has experienced similar trends for PCa. The number of cases reported annually increased from 621 in 1971 to 1312 in 1990 (Black R: Personal communication). Deaths from the disease increased from 381 men in 1971 to 645 men in 1990 (Registrar General Scotland 1972, 1991).

Except that screening for PCa is not yet endorsed in the United Kingdom in general (Boyle 1997), reasons for the trends of PCa in Scotland are likely to be those discussed above. The Scottish population is ageing and men are now living longer than their predecessors (Registrar General Scotland 1991). The frequency of TURPs done in the treatment of BPH increased dramatically during the seventies and became the main surgery for this illness (Duncan and Garraway 1993). Improvement of reporting could be indicated from previous reports. An early report on coverage by the advisory committee on cancer (Planning Council, 1979), estimated 15 per cent under-reporting for all cancer sites at that time. Black et al (1993) suggest that the Scottish Cancer Registry (SCR) has then approached 95 per cent completeness.

Artefactual influences of these factors on the PCa trend in Scotland are acknowledged by scientists from that country (Wilson 1987; Chisholm 1986). However, direct evidence and quantitative estimates of their relative contribution, and the contribution of a possible genuine risk component, are important for rational understanding and interpretation of PCa trends in Scotland. While age-standardisation

of annual incidence rates of the study period can give an estimate of the trend that is due to ageing, determination of the effects of improved reporting and TURP requires specific studies.

Attempts to estimate the trend of reporting efficiency are lacking. The contribution of TURP for BPH to the PCa incidence trend has been estimated using published frequency of incidental cancer among BPH patients treated with TURP. This extrapolation however has a disadvantage that the frequency of incidental PCa at BPH may vary with place and time for various reasons, most important of which is the pathological examination protocol. Some pathologists may be more keen to examine the whole prostate specimen (step-sectioning) (Newman et al 1982). This yields more cancers than examination of a sample of the specimen (Denton et al 1965). However, in an opinion survey, the majority of pathologists in the USA seem to be satisfied with examining the entire specimen if it is small (=<10 grams) and a sample if it is larger (Golimbu et al 1981). Similar practice is followed by pathologists in Scotland (Brown I; Lang S: Personal communication).

Given all this, extrapolation of the frequency of unsuspected cancers detected from TURP specimens may not always be safe. Reliable estimation of the effect of TURP on the trend can be achieved by identification and estimation of the trend of these unexpected cancers.

In the light of the above, this study attempts to investigate the rising trend of prostate cancer in Scotland, in order to determine the proportional contribution of each of its artefactual and true components. In this respect the anticipated major contribution of transurethral resection operations will be determined by analysing the trend in TURP-detected clinically unsuspected cancer cases, and in clinical cancer cases

diagnosed during the period from 1982 to 1990. Records of PCa cases available at the registry (SMR6) and the general hospital discharge records (SMR1) will be linked to assess completeness.

CHAPTER II

AIM AND OBJECTIVES OF THE STUDY

1. AIM OF THE STUDY

The aim of this study is to examine the temporal increase in prostate cancer incidence in Scotland with the intention of estimating the artefactual and the true components of the trend during the period 1982-1990.

2. OBJECTIVES OF THE STUDY

2.1 Analyse the trend of prostate cancer registrations (incidence) and mortality in Scotland during the period 1971-1990, by time, and across age, and to generate hypotheses on possible causes.

2.2 Estimate the percentage of total increase in reported incidence of PCa in Scotland that is due to ageing.

2.3 Estimate completeness of reporting of PCa and hence the increase in the reported incidence in Scotland that is due to improved reporting during the period 1982-1990.

2.4 Estimate the incidence rate of TURP-detected incidental PCa cases during the period 1982-1990 in Scotland.

2.5 Estimate the incidence rate of clinically-apparent PCa cases during the period 1982-1990 in Scotland.

2.6 Estimate the percentage of the total increase in reported incidence of PCa in Scotland that is due to the increase in TURP-detected incidental cases.

2.7 Estimate the percentage of total increase in reported incidence of PCa in Scotland that is due to the increase in clinically-apparent PCa cases.

CHAPTER III

METHODS

The thesis will achieve its objectives through a number of studies described briefly here.

1. ROUTINE DATA STUDY

1.1 Counts of all and of histologically-verified reported cases of PCa, and number of TURP operations performed for men with BPH were obtained from Information and Statistics Division (ISD) of the National Health Services. Counts of deaths from PCa and of the Scottish male population were obtained from the series of the Registrar General Scotland annual reports.

1.2 Annual and five-year average incidence and mortality rates, and annual TURP rate were calculated from 1971-1990 using mid-year estimates of male population. Rates were adjusted for age by direct standardisation using 1981 census population for Scotland as standard.

1.3 Trends over time for rates, incidence to mortality (I/M) ratios, and percentages of histologically-verified cases were described and inferences were made about the plausible causes of the trend in the incidence. See chapter VI.

2. A STUDY OF REPORTING COMPLETENESS

2.1 For this, and the following study, a master data file was prepared by the ISD, containing all Scottish Cancer Registry (SMR6) records for men registered with PCa, and hospital discharge (SMR1) records (the first record in each case) for every patient with a diagnosis of PCa or BPH or TURP operation during 1981-1990. These records were linked.

2.2 These data provided two sources of PCa ascertainment. The capture-recapture method was used to estimate the number of cases that were unknown to the two sources and thus completeness of cancer registration and the total number of cases in the period 1982-90 (see chapter VII).

3. ESTIMATION OF THE TREND IN TURP-DETECTED INCIDENTAL CASES

This was accomplished in steps in the following order:

3.1 Field-work study

3.1.1 A data file for Lothian similar to the master file (see 2.1) for the whole of Scotland, but with patient's identification information, was prepared by ISD.

3.1.2 From this, one hundred and seventy-two cases were selected for a case-note review as possibly incidental on the basis of one of the following criteria: (a) the time from the TURP operation to the date of diagnosis (SMR6) or admission date (SMR1)for PCa was between 0 and 6 months; (b) BPH diagnosis was recorded on one SMR1. The selected cases were restricted to be 55-79 years old and diagnosed in the years 82-84 or 88-90.

3.1.3 Case-note review was undertaken to determine whether these cases were incidental so far as possible.

3.1.4 Cases were divided into four groups according to criteria available from SMR1's and SMR6's (see 3.1.2- these will be called "SMR-incidental variables" and derived case-groups "SMR-incidental groups"). For each of the SMR-incidental groups the conditional probability of a case being incidental was estimated as the proportion of cases found to be incidental from the case note review (see chapter VIII and appendix E).

3.2 Application to routine data for Scotland

3.2.1 Reported cases in Scotland in each of the periods 82-84, 85-87 and 88-90 were divided into two age groups (0-64 and 65 or more years) and classified into SMR-incidental groups.

3.2.2 The unconditional probabilities of cases being incidental were estimated from the conditional probabilities for each SMR-incidental group (see 3.1.4). This was done separately for each age group and time period.

3.2.3 The age-specific unconditional probability is then applied to numbers of reported cases in each age group to estimate the number of incidental cases.

3.2.4 For each of the three periods 82-84, 85-87 and 88-90, age-specific incidence rates of TURP-detected incidental PCa and clinically-apparent PCa were estimated using counts from 3.2.3 and mid-year population estimates for males in Scotland.

3.2.5 Rates were adjusted for age and the percentage increases with time in the later periods were calculated (refer to chapter IX).

4. ANALYSIS OF THE MAIN COMPONENTS OF THE INCIDENCE TREND

4.1 Keeping age-specific incidence rates fixed through the study period, the absolute and relative (%) increase in the reported registrations from 82-84 that is due to the change in population structure (ageing) was estimated.

4.2 The percentage increases in incidence due to completeness of reporting and to the rise of incidental cases, obtained as in the above, were applied to the number of registrations, after allowing for ageing to yield the absolute and relative increase in registrations due to these two components.

4.3 From these, the relative contribution of ageing, completeness and TURP components to the total increase in the reported registrations between 1982-84 and 1988-90 was derived. It follows that the genuine (non-artefactual) component can also be estimated (see chapter IX).

5. CONFIDENTIALITY OF DATA

In compliance with data release and confidentiality regulations, necessary formalities for obtaining the data for this study were followed and respected. Applications were sent to the ISD defining types of data requested and the purposes of their use in the study. Permissions were obtained from urologic and general surgical consultants who have been looking after PCa patients in Lothian region hospitals. Medical record officers in the concerned hospitals were informed of the consultants' permissions and arrangements were made with them before conducting the case note review.

Data obtained from the ISD and clinical notes were treated as strictly confidential. They were stored on the mainframe computer system of the Public Health Sciences Department. Access to the department system is normally monitored and protected by personal passwords assigned to eligible users. Finally, arrangement has been made to destroy the data as soon as the purpose of their use is accomplished.

CHAPTER IV

LITERATURE REVIEW

1. BACKGROUND AND NATURAL HISTORY

1.1 Background

The prostate gland is a firm, partly glandular, and partly fibromuscular organ surrounding the first portion of male urethra. It is triangular in shape. The broad base is directly adjacent to the bladder neck and the apex is directed downward (Kovi 1989). McNeal (1989) has identified three anatomical zones in the gland; peripheral, central and transition zones. The peripheral zone is the largest comprising nearly seventy-five percent of the glandular tissue, followed by the central zone which comprises about twenty percent.

For practical reasons, researchers sometimes use simpler anatomic divisions like, transition zone versus non-transition zone (McNeal et al 1990), and outer gland, comprising peripheral and central zones, versus inner gland, formed of transition zone (Lee et al 1991). Some pathologists were unsatisfied with McNeal's divisions and their terms, and they particularly do not admit the possibility of distinguishing between the transition and central zone. They rather named three portions of the gland; the posterolateral, anterior and periurethral portions, which seemingly correspond to McNeal's peripheral, central and transition zones (Mostofi et al 1992).

Whatever terminology is used, the importance of these anatomic divisions for the study of prostatic cancer is beyond doubt; since its site of origin within the gland could determine its clinical presentation, and method of its detection and diagnosis.

1.2 Presentation

Prostate cancer is adenocarcinoma in more than ninety percent of the cases (Nomura and Kolonel 1991). In a consecutive series of prostatectomy specimens 68 per cent of PCa originated from the peripheral zone, 24 per cent from the transition zone and 8 per cent from the central zone (McNeal et al 1988a). This predilection of PCa to the periphery of the gland has also been noticed in other case series (Franks 1956) and in an international autopsy study (Breslow et al 1977).

Prostate cancer presentation can be classified in three ways; "latent", "incidental" and "clinical" carcinoma. Latent carcinoma is PCa discovered on postmortem examination of patients who had no symptoms or signs of the disease during their life (Mostofi et al 1992). Although, some latent carcinomas were found to be infiltrative, it was suggested that their growth rate potential was low so that they were not clinically manifested (Yatani et al 1982).

Incidental PCa is clinically inapparent cancer discovered incidentally upon examination of prostatic tissue removed surgically for a presumed benign prostatic obstruction (Kovi 1989; Mostofi et al 1992), or by needle biopsy performed because of elevated PSA without suspicious digital rectal examination (DRE) or transrectal ultrasound (TRUS) (Schroeder et al 1992). We note that Franks (1973) described latent carcinoma as an incidental finding at autopsy. While this is true, it was necessary to distinguish between carcinomas discovered at autopsy and those incidentally found during life. Autopsy cases have the common characteristic of latency. The majority of incidental PCas discovered at TURP to treat BPH are

localised and small, but some are true clinical of advanced stage (Corder et al 1994; Cantrell et al 1981). Therefore, it was sensible that scientists agreed to reserve the term latent for cancers found only at autopsy (Chisholm 1986).

Clinical PCa includes cases in which DRE reveals a nodule, induration or asymmetry (Mostofi et al 1992). Once prostate cancer is suspected, histological verification is required to confirm the diagnosis (Catalona and Scott 1978; Franks 1973). Prostatic acid phosphatase (PAP), ultrasound and other investigations are considered as other methods of detecting clinical PCa but it has to be confirmed by biopsy (Mostofi et al 1992). "Occult" PCa is unsuspected prostatic carcinoma which becomes clinically manifest by its metastasis (Kovi 1989). Prostate cancer has been seen with invasion of the prostatic capsule and the surrounding lymphatics and venous plexuses when the tumour is still small causing no symptoms or signs of the disease (Franks 1956). These cases are detected by biopsy of bone or lymph node in a patient who has had no symptoms of prostatic disease. The prostatic origin of these metastatic lesions is demonstrated by elevated PAP and/or PSA serum levels and confirmed by a prostatic biopsy (Mostofi et al 1992).

It is therefore clear that of the total prostate carcinoma occurring in men, clinical PCa is the fraction that manifests itself. Occult PCa is a form of clinical PCa presenting itself in a different way (by its metastases) and incidental PCa is an outcome of technology (TURP) and pathologists' curiosity, some of which would be potentially latent and some might have progressed to clinical disease (Sheldon et al 1980; McNeal et al 1988a). Latent PCa is the fraction that passes unnoticed during life and is disclosed only if autopsy is carried out.

1.3 Diagnosis

Most commonly, prostate cancer patients present with symptoms of urinary outflow obstruction. In some series this can affect 70% of patients (Chisholm 1986). These symptoms however, can not distinguish between BPH and cancer (Buck 1995), and the idea that they are of shorter duration in the case of malignancy could not be supported (Chisholm 1986).

Some patients present with haematuria and in about 10 to 15 percent, the only symptom is bone ache suggesting bony metastasis (Buck 1995). While these are more specific for cancer, they are manifestations of late stage.

In United Kingdom, about two-thirds of patients present with locally advanced or metastatic disease (Viswanth et al 1993). Rana et al (1993) reported that more than half of the cases diagnosed in their prostate clinic presented with clinically advanced stage. This compares unfavourably with the American figures which showed that 40 percent of their patients present with such stage (Schmidt et al 1986).

Symptoms usually initiate digital rectal examination (DRE) and other investigations and diagnosis is then established by biopsy of the prostate.

1.3.1 Digital rectal examination (DRE)

This is the only means of examining the prostate physically. Before 1920, it was the only diagnostic test which could elicit biopsy for confirmation (Guinan et al 1980). After that, diagnostic procedures increased in number and became more accurate.

The normal prostate felt on DRE, as described by Babayan (1989) is "..... a smooth bipolar organ, which is roughly the size of a chestnut with a consistency similar to that of the thenar eminence of the hand.".

Irregularities in symmetry or texture of the prostate should raise the possibility of malignancy (Babayan 1989), and the earliest palpable change suggestive of cancer is conventionally known to be a discrete nodule of a firm or stony consistency (Prout 1973).

However, the DRE diagnostic efficiency is hampered by certain limitations. The DRE finding is a subjective interpretation of the examiner and depends largely on his experience (Smith and Catalona 1995). Experienced urologists though, are sometimes obliged to reserve their diagnosis for certain time when they are dealing with early cancer (Denis 1995). DRE can miss more than 40% of these tumours (Catalona et al 1994a). It is also possible that DRE will miss some palpable tumours, because of their soft texture or diffuse growth (Byar et al 1972), and all prostate cancers that arise in the transition and central zones, because of their location away from the palpable field.

On the other hand, distinction between a malignant nodule and a benign nodule, caused by prostatic hyperplasia, granulomatous prostatitis or calculi, by DRE is sometimes very difficult. According to Jewett (1956) 50% of suspected nodules only will turn out to be malignant on biopsy.

Having said that however, DRE is appreciated by urologists for its simplicity, low cost and ability to detect some of these PCa cases that are potentially curable (Cupp and Oesterling 1993).

1.3.2 Tumour markers

Prostatic acid phosphatase (PAP): Prostate acid phosphatase is an isoenzyme of acid phosphatases group that occurs in greatest concentration within the prostate

but is also detectable in white blood cells, seminal vesicles and pancreatic islet cells (Babayan 1989).

Elevation of PAP serum level is mainly a manifestation of advanced metastatic disease (Babayan 1989). However, up to 20 per cent of patients with metastatic disease can be missed by the test (Chisholm 1986; Buck 1995). Its specificity is undermined by the fact that high serum levels could be seen in other diseases like leukaemia and islet cell carcinoma (Babayan 1989).

Secondaries of prostatic origin in lymph nodes, lungs, large intestine and bone have been identified by tissue staining using anti-PAP antibodies. Several techniques for the procedure have been used with results suggesting high sensitivity (Bruce and Choe 1987).

Prostate specific antigen (PSA): The introduction of prostate specific antigen as a serum marker of PCa has marked one of the most important improvements in the diagnosis of the disease. About this Stamey (1992) said that the diagnosis of prostate cancer has changed for ever. Brawer (1993) described PSA as the best marker for prostate carcinoma and may be the best tumour marker available currently.

PSA has the advantage of being an objective test. It was found more predictive for the presence of PCa than PAP (Stamey et al 1987) and DRE (Cupp and Oesterling 1993; Catalona et al 1994a).

However, its usefulness was controversial because of some shortcomings. PSA is specific for prostatic epithelium but is not cancer specific (Benson 1994). Elevation of serum PSA value above the reference range, which is indicative of cancer, can occur in non-malignant prostatic diseases such as BPH (Stamey et al 1987; Armitage et al 1988) and prostatic intraepithelial neoplasia (Brawer 1989). Conversely, some

prostate cancer patients with locally confined cancer may present with normal serum PSA value (Colberg et al 1993; Oesterling 1991). As a result, PSA was considered neither specific nor sensitive enough for prostate cancer detection (Oesterling et al 1993).

False elevation of PSA level was noticed following manipulation of the prostate by prostatic massage, TURP, transrectal biopsy or ultrasonography (Schmidt 1992; Yuan et al 1992; Stamey et al 1987). This implies that collection of a blood sample for PSA measurement should be done before or enough time after these procedures.

1.3.3 Transrectal Ultrasound

Transrectal ultrasound (TRUS) is another important landmark in prostate cancer diagnosis. It came to replace the less accurate transabdominal and transperineal approaches (Schmidt 1992). First reports on TRUS use in diagnosis of prostatic diseases have come from Japan (Watanabi et al 1975), however, initial experiences with the early generations of the instrument, in Europe during the eighties, revealed inconsistent performance; accurate results in some patients (Brooman et al 1981a; Brooman et al 1981b) and poor results in some others (Okafor et al 1983; RicKards et al 1983).

With the current technology, TRUS today is widely accepted as an effective means of PCa diagnosis (Schmidt 1992; Lippman et al 1992). It complements DRE, as it can detect cancers when they are still impalpable (Terris et al 1991), but the most popular application is TRUS-guided biopsy (Flam et al 1992). In this respect, TRUS guidance of biopsy provides greater accuracy in targeting suspected lesions (Peeling and Griffiths 1989; Flam et al 1992) and predictability of PCa compared to digital guidance (Lippman et al 1992; Liddell et al 1986).

The ability of TRUS to detect a malignant lesion in the prostate depends on the appearance of this lesion as a hypoechoic shadow in contrast with normal isoechoic tissue around it (Peeling and Griffiths 1989). A problem may arise then when we deal with cancers that are isoechoic and difficult to differentiate from normal tissue (Peeling and Griffiths 1989; Griffiths et al 1987). Nonetheless, TRUS-guided biopsy can be performed to obtain systematic samples of tissues from all over the prostate rather than just sampling the suspected lesions. The former type has been found to yield more cancer than biopsies targeted toward hypoechoic lesions (Hodge et al 1989).

Malignant tumours visible by TRUS are considered clinically apparent (Shroeder et al 1992) and defined on the basis of tumour volume are very likely to be clinically significant tumours (Terris et al 1992a). Proper assessment of TRUS diagnostic capability for PCa, however, is awaited from well designed controlled trials. Some pilot works for that have already been started (Schroeder et al 1996).

1.3.4 Bone Scan

In about 10 to 15 per cent of prostate cancer patients, the only symptoms at presentation are related to bony metastases (Buck 1995). For those, bone scanning using isotopes (Technetium) is the most sensitive means to diagnose metastasis. Its positivity for metastasis precede that of x-ray by few months to four years (Babayan 1989; Buck 1995). In a review article it has been estimated that between 10 to 50 per cent of PCa patients with negative radiography have a positive bone scan (Merrick 1975). However, bone scan is affected by high false positive results owing to similarity of malignant changes appearance with those of other bony conditions like Paget's disease. The adjunct use of radiographic skeletal survey has been found useful

in differentiating metastatic from benign changes and then minimizing the false positive rate (O'Donoghue et al 1978). Cancers suspected by bone scan needs to be confirmed by histology so that an accurate diagnosis is finally available and false positive scans will be eliminated.

Serial (annual) radionuclide bone scanning was and is still used in monitoring disease progress and its response to treatment, but after introduction of PSA in this area Buck (1995) believes that serial bone scanning is no longer a cost effective procedure.

1.3.5 Other diagnostic tests

Computed tomography (CT) and magnetic resonance imaging (MRI) are other imaging techniques that have been presented as diagnostic tests for PCa. However, their contribution is hampered by poor accuracy, high cost and high time-consumption (Flam et al 1992).

Computed tomography can display abnormalities in contour of the prostate, yet it can not identify lesions within the gland (Hricak 1988). The MRI on the other hand, produces excellent tissue contrast allowing clear delineation of intraprostatic anatomy, but its high sensitivity is coupled with high false positive rate in detecting non-palpable lesions (Carter et al 1991). The newer endorectal coil probe, as opposed to the older body surface coil, achieved promising results (Schnall et al 1989) but, the higher cost of MRI, compared to TRUS (Rifkin et al 1990) remains as the main barrier to its wider application.

1.4 Progression

It is known that between 26 and 37 per cent of men dying at fifty years old or older have latent PCa at autopsy (Breslow et al 1979; Yatani et al 1982). However,

there is a 9.5 per cent probability that a man of this age will eventually develop PCa, and a 3 per cent probability of his dying from it (Seidman et al 1985).

This disparity between the prevalence of latent foci of invasive PCa and the risk of the clinical form of the disease underlines a difference between a prostatic carcinoma that remains innocuous all through life, and that which is likely to progress and become lethal unless effective treatment succeeds in halting the progression. It is therefore challenging for scientists and urologists to identify the factor or the group of factors that determine this natural course of prostatic malignancy.

To date, the marker which can tell, before any intervention, which case will progress and which will not is still being sought (Chisholm and Habib 1993). Tumour volume or stage and grade have been recognized as most important prognostic factors (McNeal et 1986; Whitmore 1994; Gleason 1988). However, owing to methodological variation and deficiencies, observations were inconsistent, discordant and poorly validated. In a series of autopsies McNeal (1969) found that capsular involvement and perineural invasion were the most common early events of tumour growth and were directly correlated with tumour volume. These observations were further supported by findings on another series of autopsies (McNeal et al 1986), radical prostatectomies (McNeal et al 1988b; McNeal et al 1988c), and a series of cystoprostatectomies performed for patients with bladder cancer without knowing in advance whether they had PCa or not (Stamey et al 1993a). In this last series, the investigators concluded that cancers smaller than 0.5 ml are not likely to reach clinically significant size in view of the long doubling time of prostate cancer.

In some of the necropsy studies, loss of differentiation (on the Gleason grade score) was also strongly correlated with seminal vesicle invasion, capsular invasion

and metastasis (McNeal et al 1986) and to lymph node metastasis (McNeal et al 1988c). It was also correlated with tumour volume.

Information from such studies is important, but the cross-sectional design does not allow following of the time sequence of the correlated events (volume, grade and metastasis). Also they are based on selected groups of patients chosen on the bases of age, operation criteria and information availability, which could impair their generalizability.

More useful information has been obtained from follow-up studies on unselected groups of patients with PCa who received no treatment for their disease (Thompson and Chodak 1992). Unfortunately, in the light of the remarkable development in diagnostic methods following the advent of PSA and TRUS-guided biopsy, series of untreated patients from the pre-PSA and TRUS era may be incomparable with those followed because of variability in disclosing hidden and early stage cancers. Therefore, data from the first half of the century may be too old to represent today's results.

Several studies have reported on such series of patients (Cantrell et al 1981; Moskovitz et al 1987; Madsen et al 1988; Johansson et al 1989; Adolfsson and Carstensen 1991; Whitmore et al 1991), but the only population-based and largest is that of Johansson and his colleagues. This series comprised 223 consecutive patients with localised PCa, without local or distant metastases, managed by watchful waiting. Multivariate analysis showed that T-stage (hence size) of the tumour was an important determinant of progression but not of death caused by the disease. Histological grade however, was significantly correlated with both progression and death.

Although it is one of the best examples available of cohort studies of the natural history, this study has been criticized for selection bias favouring older patients and those with low grade tumours (involved in the decision to manage by watchful waiting), and for the methods used in progression assessment (Catalona 1994).

Recently, changes in PSA serum concentration have been presented as predictors of biological potential of prostate cancer with promising results. Using stored blood samples for participants of Baltimore Longitudinal Study of Ageing (BLSA) collected over 30 years, the role of change in PSA level was compared in men with and without prostate cancer up to 25 years before the diagnosis of cancer using a nested case-control study design. Men without prostatic disease showed a slow linear increase in PSA levels, whereas BPH cases exhibited a gradual acceleration in the rate of change in PSA. In contrast, cancer cases exhibited an early linear phase followed by an exponential phase of increase in PSA levels before diagnosis. The exponential phase of these increases began 7 to 9 years, on average, before tumours were detected clinically (Pearson and Carter 1994).

The deoxyribonucleic acid (DNA) ploidy status determined by flow cytometry (FCM) or nuclear image analysis and Ki-G7 monoclonal antibody have also been tried to predict progression potential (Deitch and DeVere-White 1992; McLoughlin et al 1993; Greene et al 1994), but their role is yet to be established.

In conclusion, despite the gain in knowledge, the natural history of PCa will remain to be unpredictable until valid answers about the values of various prognosis determinants are obtained and new ones identified.

2. STAGING OF PROSTATE CANCER

Cancer staging aims at description of the local extent of the neoplastic disease and its distant status in a particular patient. Accurate staging is essential for assessing natural course of the disease and deciding on the appropriate therapy. It is also essential for epidemiological studies, entry criteria to clinical trials and other research. Such accuracy depends on the precision of staging procedures and the reproducibility of any proposed classification of cases with the cancer.

2.1 Staging systems

Two kinds of staging are identified: clinical and pathological. Pathological staging is more accurate but of limited value for PCa, as it is only available when radical surgery has been performed making the comparison between different treatments extremely difficult (Benson and Olsson 1989). Clinical staging, on the other hand, is based on clinical assessment of the tumour before any treatment is started, using the available clinical data of examinations and laboratory tests (Wallace et al 1975). It is therefore this staging (clinical) which is highly demanded by urologists to help them understand the natural course of their patients' disease and make the right decisions about their therapy.

Four clinical staging classifications are currently advocated for prostatic adenocarcinoma. The Whitmore-Jewett system, the Tumour Node Metastasis (TNM) system of the International Union Against Cancer (UICC), the American Joint Committee (AJC) system, and the more recent staging classification proposed by the Organs Systems Coordinating Centre (OSCC) of the National Institute of Health (Graham 1992).

The Whitmore-Jewett staging was developed by Whitmore in 1956 in which prostatic adenocarcinoma was grouped into four categories (A-D or I-IV) depending on the results of DRE, pathological examination of presumed benign surgical specimens and metastatic evaluation (Whitmore 1956).

Stage A (I) is defined as a prostate cancer that is not clinically suspected either by DRE or laboratory tests, and is found only on pathological examination of a prostatic tissue. Stage B (II) represents the earliest truly clinical stage and comprises cases in which cancer is confined within the prostate and suspected by presence on DRE of a more or less circumscribed area of induration. Stage C (III) is clinically manifest locally advanced prostatic cancer without evidence of distant metastasis. Stage D (IV) is metastatic cancer (with lymph node or other distant metastasis) regardless of the prostatic manifestations (Whitmore 1956). Therefore, this stage includes cases which are identified by their distant metastasis only (occult carcinoma).

The Veterans Administration Co-operative Urological Group (VACUG) used a similar staging system but with Roman numerals and elevated plasma acid phosphatase accepted as evidence of tumour spread even if metastasis are not evident by other methods (Mellinger et al 1967).

Based on tumour volume and grade, some modifications to Whitmore's system have been proposed mainly to refine stage A and B. Jewett (1975) suggested that stage A be further subdivided into A1 and A2 sub-stages. Stage A1 is defined as a low-grade focal lesion and A2 as a high-grade, diffuse lesions. He has also suggested subdividing stage B into B1 and B2. B1 represents cancer clinically felt to occupy less than one lobe of the prostate, including the discrete palpable nodule of firm or stony

consistency limited to a part of one lobe, averaging 1 centimetre or a little more in diameter. B2 includes tumours larger than B1 but still clinically confined to the prostate.

Other modifications to stages A and B have been proposed by Catalona and Scott (1978). They divided stages A and B each into three subcategories; (A_f, A_1, A_2 and B_{1n}, B_1, B_2). A_f is a focal carcinoma, A_1 is carcinoma involving one lobe of the gland and A_2 is multifocal or diffuse carcinoma. B_{1n} is a solitary nodule no more than 1.5 cm. surrounded by normal prostatic tissue on all sides. B_1 is another tumour involving one lobe of the prostate and B_2 is a tumour involving both lobes of the gland. Sheldon et al (1980) have similar designations for the subcategories of stage A with some differences in their definitions: A_f is a focal tumour involving 3 chips or less, A_1 is cancer in more than 3 chips of restricted to one or two contiguous quadrants, and A_2 is cancer in 2 non-contiguous quadrants or greater volume.

Whitmore (1980) has re-classified stage B into three subcategories from B_1 to B_3, with B_1 representing a nodule 2 cm. or less confined to one lobe, B_2 is a nodule larger than 2 cm. but confined to one lobe and B_3 is a nodule involving both lobes.

Stage D was divided into D_1 for patients initially assessed as stage A, B, or C but with proven pelvic lymph node involvement found at subsequent surgery, and D_2 for patients with metastasis beyond the pelvic lymph nodes (Catalona and Scott 1978).

While the Whitmore staging system is the most widely used classification in the United States, the TNM classification was developed by UICC and is very popular in Europe and some parts of the United States. As the name implies, this classification incorporates simultaneous description of tumour local extent (T), lymph node involvement (N) and distant metastasis (M).

Early versions of the classification contained five T, four N and five M categories. The subscript x is suffixed to T, N or M if the minimum requirements of assessment are not met (Wallace et al 1975):

T0 No palpable tumour. This category includes those cases of the incidental finding of a cancer in an operative or biopsy specimen
T1 Tumour intracapsular surrounded by palpably normal gland
T2 Tumour confined to the gland. Smooth nodule deforming contour but lateral sulci and seminal vesicles not involved
T3 Tumour extending beyond the capsule with or without involvement of the lateral sulci and /or seminal vesicles
T4 Tumour fixed or invading neighbouring structures
N0-4 Lymph node status ranging from 0 (no evidence of L.N. involvement) to 4 (juxta-regional nodes involvement)
M0 No evidence of metastasis
$M1_a$ Evidence of occult metastasis by biochemical and/or other tests
$M1_b$ Single metastasis in a single organ site
$M1_c$ Multiple metastases in a single organ site
$M1_d$ Multiple metastases in multiple organ sites

It is apparent that the T0 category of this TNM classification is equivalent to stage A in Whitmore-Jewett system.

This early edition of the TNM classification was, initially, in disagreement with the TNM classes of AJC. In 1987, the UICC and AJC were able to agree on a unified classification in which, T0 of the original UICC system was replaced by $T1_a$ and $T1_b$. $T1_a$ is for tumours of 3 microscopic foci of carcinoma or less, and $T1_b$ is for tumours of more than 3 foci. The old T1 was merged in the new T2 category which contains two subcategories ($T2_a$ and $T2_b$). Some modifications to N and M categories were introduced (Catalona and Whitmore 1989).

Urologists in Europe however, were unsatisfied with the joint classification with their criticism mainly against T categorization (Chisholm 1988; Schroeder et al 1988). As a result, a dialogue was initiated in 1989 between representatives of the UICC, genitourinary group of the Organization for Research on Treatment of Cancer

(EORTC), the AJC and other American groups. The outcome was a new TNM classification acceptable to all participating parties (Schroeder et al 1992).

In this classification T1 was assigned to tumours that are clinically unapparent, not palpable nor visible by imaging. This category is further subdivided into three subcategories: $T1_a$ for tumours that are an incidental histologic finding in 5% or less of tissue resected, $T1_b$ for those that are incidental histologic finding in >5% of tissue resected, and $T1_c$ for tumours identified by needle biopsy following elevated serum PSA. $T1_a$ and $T1_b$ correspond to A_1 and A_2, respectively, of some only of Whitmore-Jewett system modifications (Cantrell et al 1981). $T1_a$ based on the percentage of resected tissue involved with cancer is now different from A_f which is based on the number of chips involved with cancer.

T2 was reserved for palpable or visible carcinoma confined to the prostate. Under this category, there are $T2_a$ tumours involving half of one lobe or less, $T2_b$ tumours that involve more than half of one lobe but not both lobes and $T2_c$ tumours that involve both lobes. T3 tumours are locally extensive carcinoma and T4 tumours are fixed or invade adjacent structures other than seminal vesicles.

The regional lymph node categories are similar to those of 1987 version (Hermanek and Sobin 1987) ranging from N0 for absence of metastasis to N3 for metastasis more than 5 c.m. in greatest dimension. N1 is metastasis in a single lymph node 2 c.m. or less in greatest dimension and N2 is for metastasis in single or multiple lymph nodes 2-5 c.m. in greatest dimension.

The distant metastasis category M1 has been subdivided into three subcategories: $M1_a$ when non-regional lymph nodes are involved, $M1_b$ when bones are involved, and

$M1_c$ involvement of other sites. When more than one site of distant metastasis present the most advanced is taken for staging (Hermanek and Sobin 1992).

TNM status was again related to tumour grade to produce a summary stage grouping ranging from stage group 0 for $T1_a$ N_0 M_0 G1 to stage group IV for tumours with any T and $N_{1,2,3}$ or M1 (Schroeder et al 1992).

The OSCC staging system incorporates features from both TNM and Whitmore-Jewett systems. Incidental PCa is designated as TA which is subdivided into TA1 and TA2 on the basis of the 5% involvement with cancer of the resected tissue, similar to $T1_a$ and $T1_b$ of the TNM system. Palpable tumours confined to the prostate are designated as TB1,2,3 corresponding to $T2_{a,b,c}$ of TNM. Locally extensive and metastatic tumours are designated as TBTC and follow nearly T3 and T4 categories in the TNM system (Catalona and Whitmore 1989).

The Whitmore-Jewett system has been appraised by a conference experts committee on staging of PCa, for its simplicity, but the committee has considered it inadequate for describing local tumour extent and that the multiple alterations are often confusing (Graham et al 1992). The confusion in Whitmore-Jewett system does not stop at variability in substaging A and B stages, but has included the quantitative criteria distinguishing substages A_1 from A_2. This varied between those who used the percentage of resected tissue involved with tumour to those who used number of chips or foci of carcinoma. Of those who used the percentage, some used the 5% (Cantrell et al 1981; Epstein et al 1986) and some others used 50% as a cut-off (Donohue et al 1977). The number of chips in A_1 tumours varied from less than three to 5 chips involved with tumour (Eble and Epstein 1990).

A common failure of these systems is the awkward worse prognosis for cases with A_2 tumours compared to those with B_1 tumours (Golimbu et al 1978), which may indicate an under-staging problem in stage A tumours. These cases are most commonly staged on the basis of TURP specimens in which the possibility of co-existing residual tumour is sometimes high (Egawa et al 1991).

The last edition of TNM classification is a victory for PCa staging, as it gathered scientists from the two major schools (European and American) after a long history of dispute. This would minimize significantly variability in stage definitional criteria which afflicted Whitmore-Jewett system and would improve comparability of results on stage prognostic value.

The system is also an advancement compared to old Whitmore-Jewett and OSCC systems, as incorporation of imaging (TRUS, MRI and CT scan) in distinguishing incidental tumours (T1/A) from higher stage tumours would result in upstaging of some cases defined by old staging systems as incidental. And, because tumours detected by TRUS are very often clinically-significant (Shinohara et al 1989), the awkward poorer prognosis in $T1_b$ (A_2) tumours compared to B_1 tumours could partially be adjusted.

Imaging techniques are also expected to have an important role in accuracy of tumour volume measurement (Hricak 1988; Graham et al 1992; Ohori et al 1994), despite negative results from some clinical observations (Rifkin et al 1990; Terris et al 1992b).

In a consensus meeting a panel of experts acknowledged the stage grouping of the new TNM system, particularly for inclusion of grade to differentiate between

focal tumours that are well differentiated and those that are moderately or poorly differentiated (Schroeder et al 1992).

However, some deficiencies will remain awaiting further developments. Errors inherited in staging TURP specimens will continue, may be to a lesser extent than in old systems, to confound prognosis results by stage. The 5% cut-off of $T1_a$ tumours has been criticized for being confined to one institute's experience (Eble and Epstein 1990).

Lymph node staging has been and is still problematic. Pelvic lymphadenectomy is the gold standard means to determine the spread of PCa to regional lymphatics. However, its value does not overweigh its invasive nature and post-operative complications, and the less invasive alternative techniques, primarily lymph node aspiration cytology, lymphangiography and the imaging techniques, have yet to prove their accuracy in detecting lymph node involvement with cancer (Kavoussi 1994). This may not be of much concern to the urologists in the United Kingdom who are not enthusiastic about lymphatic staging. perhaps, due to a preference for radiotherapy rather than radical surgery to treat confined disease, in which irradiation of the regional lymph nodes is routine (Peeling et al 1986).

3. TURP-DETECTED INCIDENTAL CARCINOMA (Stage $T1_{a,b}$ or A)

TURP-detected carcinoma is an incidental carcinoma detected in prostatic tissue removed by TURP for treatment of clinical BPH (Whitmore 1956). Obviously, incidental carcinoma can be detected in specimens removed by open surgeries for

BPH as well. It is a matter of the prevailing urological practices, surgeon's skills and preference, and patients' condition.

Before TURP was developed and established as a time-saving and safer operation - that was nearly until the middle of this century - benign enlarged prostates used to be removed by open prostatectomies. Following early reports of its lower rates of complications and immediate mortality, compared to open operations, TURP became the standard procedure for treating benign prostate disease in the United States early in the second half of the century. Adoption of the new technique by the British surgeons came later from the first generation of urologists who travelled to USA to learn the procedure (Blandy 1978). Today, TURP has become the dominant operation for BPH in many countries (Fujita 1988; Duncan and Garraway 1993; Ball and Powell 1982; Holtgrewe 1990) but even so, open surgeries remain the first choice when dealing with very large volumes of prostate and some surgeons may prefer these approaches, especially the retropubic venue which was very popular in the UK until the early seventies (Martin 1973).

Detected by TURP or other prostatectomy, PCa is the same incidental carcinoma that is of peculiar significance to the study of the disease's natural history and treatment efficacy. These cancers represent the earliest diagnosed stage of prostate cancer and thus, have been the starting point in studies of evaluation of disease progression, either as uncontrolled series of cases (Johansson et al 1989; Rana et al 1993; Zhang et al 1991), or as part of randomized controlled trials of assessing the effectiveness of radical surgery (Madsen et al 1988) or radiotherapy (Medical Research Council Prostate Working Party 1994) against no treatment.

The importance of TURP in the detection of these carcinomas lies in the popularity of this operation during the last 3 decades and its impact on the natural course of the disease. The Scottish experience with prostatectomies for BPH in the early seventies, shows that TURP was relatively most common accounting for between 66% and 68% of these operations done in 1969 through 1974 (Graham 1977). In another report from the country the number of TURP operations done for BPH has nearly doubled (from 2243 to 4450) between 1971 and 1989, and in this last year TURP represented 94% of all prostatectomies performed for treating BPH. This trend in TURP rates has been accompanied by progressively declining trend in rates of open surgeries (Duncan and Garraway 1993). Similar progressive trends in TURP has been seen in other parts of the UK (Ball and Powell 1982), and elsewhere (Fujita 1988).

This trend has necessarily been associated with increasing detection of incidental carcinomas from the pool of inapparent disease. Between 6 to 22 per cent of BPH cases treated with TURP have been found to have incidental carcinoma (Denton et al 1965; Moore et al 1986), with an estimated average of 10% (Sheldon et al 1980). Variation is mainly related to the pathological examination protocol. Using the routine examination method Denton et al (1965) found 6 cases of these carcinomas in a 100 consecutive cases of BPH treated with TURP. An additional 9 carcinomas were found by changing to step-sectioning technique. Similarly, Lefer and Roiser (1977) have increased the detection of these cancers from 7.7 to 14 per cent by increasing the average number of blocks examined per case from 2.8 to 5.4 blocks.

Examination of all chips obtained from TURP has been recommended, by Newman and his colleagues (1982), because of its higher detection rate of these

carcinomas (14.2%) compared to examination of portion of chips (8.6%). Murphy et al (1986) have studied the inverse relationship between the amount of tissue examined to the probability of detecting stage A carcinoma and found that histologic sampling of 12 grams of randomly selected prostatic chips detected almost 90 per cent of incidental carcinoma including all "clinically important" neoplasms. Moore et al (1986) have studied this probability in relation to the number of fragments involved by tumour. They found that 95 per cent probability of detecting carcinoma in TURP specimens can be achieved by examining a minimum of 95% of the fragments if one fragment contains a carcinoma, 63.1% of the fragments if three fragments contain carcinoma and 25.8% of the fragments if 10 contain carcinoma.

Pathologists and professional groups in different institutions or regions usually make the decision regarding examination protocols and variability may exist affecting the rate of detection of the incidental PCa and therefore comparability of incidence trends among places or with time. However, examining every chip as advocated by Newman et al was criticized for being impractical (Chisholm 1986). In a survey among pathologists from USA, the majority will section every chip when the specimen weighs less than 10 grams but, only 12 per cent will carry out this way when the specimen is greater than 10 grams, while the others will use a random section technique (Golimbu et al 1981).

Another potential area of variability is the criteria of malignancy. Pathologists must decide which case is malignant and which is not, and the criteria for border line cases may differ systematically between them (Ashley 1965).

There may also be a role for the surgeon to enhance cancer detection by carefully sampling, during the operation, the posterior and peripheral tissues of the prostate

which are most likely to be the source of cancer and by sending to the pathologist tissues in which changes in characters (colour, texture) could be a sign of malignancy (Chisholm 1986).

Reporting of disclosed incidental PCas has caused an apparent increase in the reported incidence (Potosky et al 1990; Beckner et al 1985; Corder et al 1994; Alexander and Boyle 1995). However, the future of this influence will be determined by two factors: the future of TURP as a first choice treatment for BPH and the spread of PSA-based screening.

Considering the dissatisfaction among patients treated with TURP and the reports on the long term relatively high mortality after TURP (Roos et al 1989; Hargreave et al 1996), more effective and safer methods are required. Studies are being carried out on drug therapy (Oesterling 1995) and some new techniques of removing the prostate namely: transurethral microwave thermotherapy and laser ablation of the prostate (Kirby et al 1993; Bdesha et al 1993; Norris et al 1993). However, the efficacy and safety of these alternatives are not proven yet, and TURP is likely to continue to be the first choice therapy for BPH for a while (Bishop 1993).

The widespread implementation of screening using PSA and TRUS-guided biopsy procedures in the USA in the late eighties was associated with a rising PCa incidence trend and a declining trend of the rate of TURPs performed for treating BPH (Potosky et al 1995). These trends and the increase in the frequency of radical prostatectomy operations for localised cancer (Lu-Yao et al 1993) suggest that the role of TURP in PCa detection was diminishing and screening-detected cases were increasing. This was shown in the data presented by Mettlin et al (1993) where the percentage of cases in which TURP was used in the diagnosis of PCa has dropped

from 56 percent in 1984 to 40.8 percent in 1990, and PSA usage climbed from 5.8 to 68.4 percent. However, this is not true yet in the European countries who have just started screening feasibility studies; it will take some time before screening influences on the disease trend can be seen there.

4. SCREENING

Screening has applications both in the clinical and public health or preventive medicine (Boyle et al 1993). What concerns us here is the screening of asymptomatic individuals by applying examinations, tests or procedures in order to sort out apparently well persons who are likely to have the disease from those who probably are not.

Wilson and Jungner (1968) have outlined criteria to be met if screening is to be considered for any disease. Applying these criteria to the case of prostate cancer, the disease is widely recognized as an important health problem (Boyle et al 1993; Roberts 1994; Porter et al 1996), yet the issue of screening is still controversial.

Concerns have been raised about the poor performance of the available screening tests (Austoker 1994; Holland 1993). DRE was described as not sufficiently sensitive or specific (Kramer et al ,1993), especially for organ confined and potentially curable disease (Austoker 1994) and poor as a first-line screening method because of its low sensitivity (Bentvelsen and Schroeder 1992).

Serum prostate specific antigen (PSA) test appeared more promising. Using stored serum samples collected from men 10-20 years before diagnosis of PCa Parkes et al (1995) showed that PSA is a highly discriminatory screening test for prostate cancer among healthy men. Findings of a multi-centre trial involving 6630 male

volunteers showed that PSA (with the upper limit of normal value was set at 4.0 ng/ml) had higher detection rate (4.6% versus 3.2% for DRE) and a PPV value of 32% that was higher than that (21%) for DRE (Catalona et al 1994a). Furthermore, this and some other studies (Mettlin et al 1996; Schroeder et al 1996) showed that DRE screening efficiency can be improved if its abnormal findings are correlated with PSA results giving higher PPV and detection rates than when they were used each alone.

Some modifications to PSA values have been suggested to improve the low specificity in particular. Oesterling et al (1993) have studied PSA levels in 471 men who have been confirmed to be free from PCa using PSA, DRE and TRUS. They found that PSA level was significantly correlated with age and prostate volume. The same correlation with age has been observed in a study by Dalkin et al (1993). Accordingly, the age-specific ranges of Oesterling rather than the single range of 0.0-4.0 ng/ml has been recommended as reference ranges. However, application of these age-specific ranges would lead to some locally confined cancers to be missed (Catalona et al 1994b).

Based on the correlation between tumour volume and PSA level and the disparity in PSA rate per gram (gm) of volume between BPH and cancer, 0.3 and 3.5 ng/ml/gm respectively (Stamey et al 1987), another modified marker (PSA density) was compared with PSA serum concentration but the results were contradictory. While Benson et al (1992) found PSA density useful in distinguishing BPH and prostate cancer, Catalona et al (1994c) found that the use of PSA density has improved the specificity at the cost of the sensitivity and PSA concentration was particularly more

predictive than PSA density in patients with intermediate PSA levels (4.1 to 9.9 ng/ml). Part of this inconsistency has been attributed to the difficulty of estimating the gland volume accurately (Catalona et al 1994c) and part of it is undoubtedly methodological mainly due to differences in study populations.

Transrectal ultrasound (TRUS) is superior to DRE in that it can detect the small impalpable tumours (Terris et al 1991). Lee et al (1988) examined 784 self-referred men and found that TRUS had a detection rate of 2.6% which was twice as that for DRE and had higher sensitivity calculated using an assumed prevalence. TRUS was also shown to improve the DRE and PSA detection capability (Lee et al 1988; Cooner et al 1990; Mettlin et al 1996). Studies from Europe showed that the procedure was acceptable to most of patients (Collins et al 1993; Aus et al 1993), but its relative low specificity, invasive nature and high cost are against its wide use for screening (Boyle et al 1993).

The natural history of the disease is still not well understood (Alexander 1997), and until the awaited prognostic test to distinguish the clinically significant and insignificant tumour becomes available, the potential exists in prostate cancer screening for detection of clinically insignificant tumours (overdiagnosis) and thus for over-treatment (Kramer et al 1993). Another main deficiency is the lack of conclusive evidence on superiority of treatment by radical prostatectomy or radiotherapy for early stage disease compared to the wait-and-see policy and on the benefit of screening in reducing mortality from PCa. This will wait for results of randomized controlled treatment and screening studies, without which scientists find it difficult to recommend screening as a public health policy (Shroeder and Boyle 1992).

Despite these unfavourable observations and critiques some proponents of screening believe that prostate cancer meets nearly all the criteria for screening and while the previous concerns are valid important social and public health issues such as potential savings in expenditure for terminal cancer care also need to be considered (Littrup 1994). A general physician-based opinion suggested that the reduction in mortality and morbidity achieved from other cancers, such as breast and cervix, can be extrapolated to prostate cancer (Porter et al 1996).

Against this background prostate cancer screening studies have been initiated in some developed countries, mainly the U.S.A and Europe (Schroeder 1995).

Large-scale screening trials among apparently healthy men are expected to cause an apparent increase in the trend of the reported incidence due to detection of cases from the prevalence of inapparent cases. This artefactual increase is important to consider in interpreting incidence trends but as widespread detection is rarely achieved rapidly, this effect will be gradual and thus difficult to measure and evaluate (Muir et al 1994).

Screening is presumed to improve survival but part of this improvement is likely to be artefactual due to two types of biases: lead-time and length bias (Kramer et al 1993; Boyle et al 1993). The lead-time bias occurs when diagnosis of PCa is made earlier than the time the clinical diagnosis would have occurred extending falsely the period during which the patient is aware of his disease without changing the time of his death. Screening programmes involving apparently healthy men tend to identify cases with a long preclinical phase who also tend to have a long clinical phase and thus likely to have a better outcome regardless of screening, inducing an artefactual improvement of survival called the "length bias".

On the other hand Enstrom and Austin (1977) have drawn the attention to the opposite effect (decreasing effect) of cases diagnosed in the in-situ stage on survival if it was calculated on the basis of patients with invasive cancer only, in which case the in-situ cases are not included.

5. CANCER REGISTRATION

5.1 History

Mortality data accumulated over time have been and still are a rich sources for studying the trends of cancer. However, these data are usually deficient for slowly growing or rarely fatal cancer and can be influenced by the improvement in cancer treatment, and therefore, cannot replace reliable incidence data.

The need for improved data on the spread of cancer in the population was noticed in Europe at the turn of the century. Early attempts were in the form of questionnaires or adhoc surveys and the first (oldest) cancer registry in existence today is that of Hamburg (Germany) which started in 1927 as a follow-up system for patients diagnosed with cancer (Wagner 1985). Similar type of registries (patient's follow-up system) has been established in the UK in the thirties (Polock 1994; Muir 1993).

Modern registries with epidemiological purposes were established shortly before and during the Second World War. In the USA the first cancer registry was set up in Connecticut in 1936 (Connelly et al 1968). The first registry in Canada was initiated in the province of Saskatchewan in 1944 and in Europe registries were started in Denmark in 1942 and Belgium in 1943 (Wagner 1985). In England and Wales a national scheme of cancer incidence data started in 1945 (Swerdlow and Silva 1993)

and the Scottish Cancer Registry was reorganized in 1958 to become a national population-based registry (Muir 1993).

At that time, scientists began to realise the importance of having uniform nomenclature and classification to help comparability of cancer statistics collected by each registry. This was translated into a recommendation, by scientists who met in Copenhagen (Denmark) in 1946 to establish an international body whose duty is to correlate the data and statistics obtained in each country and to propose a terminology and methods of classification and tabulation. This call received the attention of the World Health Organization (WHO), which assisted the establishment of several epidemiologically-oriented cancer registries (Wagner 1985). Moreover, as a result of the continuous efforts of some scientists, particularly those of Dr. Segi, from Japan, a meeting in 1966 there witnessed the birth of the International Association of Cancer Registries (IACR) (Aoki and Kurihara 1994). The creation of cancer registries continued all over the world as can be seen from the list of countries participating in volume VI of *Cancer Incidence in Five Continents*, which is the 6th of cancer incidence monographs published by WHO collaborating centre for research on cancer (IARC) in collaboration with IACR (Parkin et al 1992).

5.2 The role of the cancer registry

Cancer registration is the process of continuing systemic collection of information on the occurrence and attributes of reportable cancer cases (Maclennan et al 1978), and the cancer registry is defined as "... an organization for collection, storage, analysis and interpretation of data on persons with cancer." (Muir et al 1985). Two types of registries are identified, hospital and population-based depending on the scope of work. While the hospital registry is primarily concerned with

improving the care of cancer patients in a hospital, the population-based registry is mainly concerned with assessing the impact of cancer on the community but, some registries have mixed functions (Maclennan et al 1978).

The cancer registry in its wider scope, being multi-functional, can serve in many areas. Most importantly, its data are invaluable for planning of health care services and for planning and evaluation of cancer control programmes (Muir and Nectoux 1977).

If cancer cases detected by screening are notified to the registry and identified as such, the registry will be in an ideal position to assist in evaluating the effectiveness of screening in reducing cancer mortality.

Case-survival can better be assessed from a cancer registry notified of all cases than from a clinical trial on a selected sample of patients, although the randomized controlled trial is preferable for comparing treatments. The registry provides researchers with a generous source of cancer cases from which they can withdraw unbiased samples for specific research (Muir et al 1985). To achieve these roles, the registry must be able to record all cases diagnosed in the community (population-based) and keep the high quality of data.

5.3 Quality of data

The two main aspects of cancer data quality are, (a) completeness; and (b) validity.

5.3.1 Completeness

Completeness is referred to as the proportion of all cases in the target population which appear in the registry database (Goldberg et al 1980). Inadequate completeness

can be over-registration (duplicate registration) but of most concern is the under-registration due to failure to identify and include all incident cases (Parkin and Muir 1992).

Therefore, the registry should be prepared to identify and minimise the problem by following active case-finding and multiple source reporting procedures. Record linkage is a useful tool that can be used to deal with duplicate registrations. Competence and familiarity of the staff with the record systems have been suggested as influences on completeness (Zippin and Lum 1993). Completeness can also be related to the readiness of physicians to notify the registry of any case they see in the clinic (Doll and Petto 1981).

Goldberg et al (1980) described three methods for measuring completeness of a registry: (a) death certificate method; (b) independent case ascertainment method; and (c) historic data method.

In the death certificate method completeness is measured as the proportion of registered cases which are not first identified by a death certificate. This uses only internal cancer registration data.

Completeness measured by the independent case ascertainment method requires an independent source of information on cancer cases against which the registry is compared. This can be another system, or an intensive survey which is the most definitive but expensive procedure. It is possible however that some cases will be unknown to all of the involved sources and assessors of registry completeness have been using a technique known as the "capture-recapture method" which gives an estimate of those unknown cases (Robles et al 1988; Schouten et al 1994; Brenner et al 1994). The technique will be explained in detail in chapter VII, starting on page 90.

The historic data method compares observed numbers of cases registered with those expected in a similar population, which is a rough measure of completeness.

The authors of Cancer Incidence in Five Continents use mortality/incidence (M/I) ratio as an estimator of completeness. The ratio is inversely related to survival so that for a cancer with good survival, such as prostate cancer, the ratio will be much lower than unity, while for cancers with poor survival this ratio will be close to the unity. A drawback of the M/I ratio as a measure of completeness however is the discrepancy in accuracy of diagnosis between mortality and incidence data, being more accurate for the latter (Parkin and Muir 1992) and the possible effect of improvement in therapy.

5.3.2 Validity

It is the second essential aspect of the quality of cancer registry data. It refers to the proportion of cases in the registry with a given characteristic (sex, age, cancer type) which truly have this attribute. Three methods have been described in evaluating data validity (Goldberg et al 1980): (a) diagnostic criteria method; (b) re-abstracted record method; and (c) internal consistency method.

Diagnosis of malignancy is the primary attribute that initiates registration. Therefore, its accuracy is the cornerstone of validity. However, diagnosis of some cancers can be a problem and prostate cancer is one of those, as some benign lesions of the gland, like atrophy and prostatic intraepithelial neoplasia (PIN), may simulate PCa (Bostwick and Srigley 1990).

However, checking over the pathologist's diagnosis of malignancy is not a common part of validity assessment in cancer registry and there would be medico-legal problems if it were. Instead, the percentage of registered cases with histologic

confirmation has been presented as an indicator of diagnosis validity (Parkin and Muir 1992). Accuracy of the other registry data are very often investigated by the ***re-abstracted record method*** in which information from clinical case notes, including pathology report, are appraised as "gold standard" against which the registry data are verified (Brewster et al 1994; Lapham and Waugh 1992; Gulliford et al 1993). Accuracy of information on primary cancer site definition, histology and their codes, and accuracy of age, sex and dates (especially the date of diagnosis) are the main subjects of validity assessments.

The ***internal consistency method*** looks for impossible codes or illegal combinations of codes (e.g. female code with prostate cancer code) in the same case record. Its value is limited to cases which are outside boundaries of prescribed logic and this does not include incorrect yet logical cases (Goldberg et al 1980).

Other indicators for validity currently in use are the percentage of cases registered on the basis of information from death certificate only ("DCO" cases) since the date of diagnosis is known to be incorrectly coded; the percentage of cases with unknown primary site "PSU" and the percentage of cases with unknown age "UnK" (Parkin and Muir 1992).

Since the reported incidence rate is a proxy measure of the risk of developing cancer, any interpretation of rates and the trends in it should consider the effect of completeness and validity of cancer registry data. The problem of incompleteness is known to be greater in the newer registries (Esteve et al 1994) and there is no doubt that cancer registry data are more accurate today than they were one decade or more back.

CHAPTER V

EPIDEMIOLOGY AND AETIOLOGY OF PROSTATE CANCER

1. DESCRIPTIVE EPIDEMIOLOGY

1.1 Prevalence of the disease

The term prevalence in relation to cancer is normally used to refer to the number of living individuals at a certain point in time who have been diagnosed with the disease sometime in the past (Feldman et al 1986). In this sense, an estimated prevalence of PCa was from 0.4% for all males to 4% for males at the age of 70 or higher (Feldman et al 1986). The prevalence in Western Europe is about 4% (Meller et al 1990). However, this is only part of the iceberg, since many men may harbour a cancerous lesion yet remain undetected till death. Several autopsy studies have been carried out to determine the proportion of this undetected cancer. This varied from 9% (Halpert et al 1963; Bean et al 1973) to 37.6% (Franks (1954). Some of the variation can be due to differences in population and pathological examination protocol (Breslow et al 1977). Following a standard protocol, Breslow et al (1977) found that 12% of men died at the age of 50 or higher had small latent cancer at autopsy and between 4.6% in the youngest and 29% in the eldest age group had medium or diffuse cancer. Yatani (1982) who also followed standardized pathological methods found latent carcinoma in 37% of the US blacks, 35% of US whites, 32% of Colombians 21% of Japanese in Japan.

The findings of autopsy studies show that the rate of prostate cancer at autopsy is much higher than the reported incidence of detected cancer - incidence rate in USA blacks was 91 per 100,000 person-years in 1985 (Nomura and Kolonel 1991), and

more importantly higher than the life time risk of detection of clinical PCa estimated at 4% (Schroeder 1993), indicating that the disease occurs more frequently than it is diagnosed or certified as a cause of death. The disparity also implies that of all men who acquire the disease, only some will succumb to clinically manifest form that needs medical attention and/or be at risk of dying from the disease.

1.2 Global burden

According to a 1985 estimate of the worldwide cancer burden, prostate cancer was the 4th leading malignancy among men with an estimated 291000 new cases diagnosed in that year. That was a 47 per cent increase over the 1975 estimate (Parkin et al 1993). The figure is expected to rise with the turn of next century even assuming stability of age-specific rates, due to the ageing population and the effect of the baby boom when they reach an age where they are at risk of PCa (Boyle 1997). In North America alone, 122,000 new cases were estimated to be diagnosed in 1991 (Boring et al 1991).

1.3 Geographic distribution

Incidence varies from one country to another. The highest incidence rate in 1983-87, adjusted to world population, was 102 per 10^5 person-years among blacks in America. The lowest incidence rate occurred in Asian countries (7.6 in Singapore) and the rates in Western Europe varied from 23 in England & Wales to 50 in Sweden (Parkin et al 1992). Nearly similar geographic variability can be observed for age-adjusted mortality rates of the disease (Coleman et al 1993).

This variability may reflect the "true" differences in the risk of prostate cancer and exposure to risk factors. However, adjustment must be made for the artefactual part that can be due differences in registration practices and efficiency, and availability

of health care services. Parkin et al (1992) have shown that countries varied in their registration completeness (measured by I/M ratio), in their cancer data validity (measured by HV%, PSU and Unk) and some countries do, but some do not, include incident cases detected at autopsy, incidentally at biopsy or cases designated as "DCO".

In contrast, an international autopsy study found the participating countries similar in the frequency of small (latent) prostatic carcinoma and the difference was in progressive carcinomas (Breslow et al 1977). This has important implications to the study of the disease aetiology. For, it means that a man's chance of developing the latent cancer is the same everywhere, but his chance of developing a progressive and fatal form of the disease differs depending on the place of living, which could signify differences in exposure to one or another risk factor as late stage determinants of disease.

1.4 Secular trends in incidence and mortality

Data for this section were taken from the monographs of Cancer Incidence in Five Continents Volumes IV, V and VI (Waterhouse et al 1982; Muir et al 1987 and Parkin et al 1992). These are in the form of age-adjusted incidence rates of prostate cancer in some countries, averaged over three to five year periods depending, probably, on availability of figures for each country. The purpose is to show and compare the direction and rate of change in four geographical regions (namely: Japan (Miagi prefecture), Scotland, Sweden and USA (Atlanta, US blacks)) with differing incidence rate levels:

Table 5.1 Trend in PCa age-adjusted incidence rate (per 100,000 men) in some countries

Country	Incidence rate by period			
	1973-77	1978-82	1983-87	% Change
USA	95.7	91.2	102	6.6
Sweden	44.4	45.9	50.2	13.1
Scotland	20.4	23.3	27.8	36.3
Japan	4.9	6.3	7.8	59.2

The period interval varied, so that the first period was 71-75 for Sweden and 75-77 for USA. The second period was 78-81 for Japan. It is evident that despite great differences in the absolute levels of rates between countries, all have increased but the percentage increase was higher in countries with lower incidence.

In a recent compilation of international data on cancer incidence and mortality (Coleman et al 1993), similar trends in truncated incidence rates (age-adjusted) have been observed in other countries. In the same report and another on cancer mortality in European countries (La Vecchia et al 1992), trends in mortality rates were variable. In most European countries, truncated 35-64 years rates have remained stable during 1970-89 around values of 5/100,000 including Scotland (and of 7-8/100000 in Nordic countries including Sweden) or have only slightly increased. However, there were generalized upward trends noted when the overall age-standardized rates were used which the authors believed to be artefacts of improving diagnosis and certification for older ages (La Vecchia et al 1992). In Japan and USA the truncated 35-74 years mortality rates were increasing between 1965 and 1985, but much more slowly than incidence rates at around 2% and 10% every five years, respectively, compared to 9-25% and 30% increases in incidence rates (Coleman 1993).

The systematic increase in the incidence rate while mortality rates are stable may indicate the increased detection of early stage cancers which tend to be less aggressive. Evidence of this has been documented in the USA (Potosky et al 1990; Mettlin et al 1993). It can also be inferred from the slight improvement in survival noticed in some countries (Black et al 1993) with no evidence to suggest improvement in treatment. Fairly recent trends in incidence in North America have been associated with aggressive use of the new diagnostic techniques, PSA and TRUS-guided biopsy (Potosky et al 1995; Mettlin et al 1993). This and other artefacts caused by improvements in reporting, changes in criteria of malignancy, improvement in accuracy of diagnosis and changes in registration and coding practices (Muir et al 1994) are important to consider in interpreting time trends. While the use of truncated rates[1] is meant to minimise the effects of the artefact of improvements in reporting and diagnostic techniques that are likely to influence trends at older ages more, these artefacts have been suggested, as seen in age-period modelling analysis, to influence the trends in younger age groups as well (Coleman et al 1993).

In the search for plausible explanations for age-specific temporal trends of PCa researchers have employed graphical and statistical modelling techniques to investigate the possibility of and quantify the birth (cohort) effect which may indicate that, regardless of age, certain birth cohorts have been particularly with a higher (or lower) risk of contracting or dying from the disease. The results were variable. In a study of mortality for PCa among the USA non-whites, Ernster et al (1978) showed,

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[1] N.B. Omission of 0-34 years from the age-standardization process in the truncated rates will lead to much increased rates but is otherwise unimportant since PCa never occurs <35 years.

graphically, that men born before 1901 experienced higher rates than those born after that. In two studies on PCa mortality trend in England and Wales the results were contradictory. In the first, Holman et al (1981) found that the risk of death increased to reach the peak in men born around 1876-1896 and decrease after that. In the second however, results of statistical modelling did not suggest any cohort effect (Osmond et al 1983). Cumulative risk of developing or dying from PCa has been estimated from the fitted age-cohort models with geographically variable patterns (Coleman et al 1993).

Despite the importance of age-period-cohort graphical and mathematical techniques in cancer trend analyses, their use has been limited because of methodological problems. Graphical methods can lead to subjective interpretation which can be avoided by appropriate modelling (Esteve et al 1994). Statistical modelling has the inherent limitation of the linear dependency of age, period and cohort, which is so often called "identification problem" (Kleinbaum et al 1982). This makes the separation of the cohort and period effects very uncertain and requires a priori knowledge of the nature of the trend components (Esteve et al 1994). Devesa et al (1995) have noted that modelling of incidence trends have the limitation of the scarcity of data for the earliest and most recently born cohorts and that when rates are increasing over all ages, it will be technically difficult to separate the contributions of the cohort and period trends to the overall trend in rates.

2. AETIOLOGY

Despite the available knowledge on various suspected risk factors the aetiology of prostate cancer is obscure. The disease is known to be of older men. It rarely

occurs in men under the age of 50 and rates increase sharply with age thereafter; more rapidly than any other cancer (Mandel and Schauman 1980).

Populations from different parts of the world experience different levels of incidence and mortality rates, and blacks in the USA have the highest incidence rate (Parkin et al 1992; Coleman et al 1993). These observations may indicate differences in genetic susceptibility to the disease. Prostate cancer has been found running in families of index cases (McWhorter et al 1992; Steinberg et al 1990), with a possibility of inheritance of a rare autosomal dominant gene (Carter et al 1993).

The search for genetic tendency to PCa was taken a step further to locate a specific gene associated with the disease. Chromosomal changes, such as the loss of chromosome 8p (Bova et al 1993; MacGrogan et al 1994), mutation of the oncogene *ras* p21 (Anwar et al 1992) and the mutant tumour suppressor gene p53 (Dinjens et al 1994) have been observed among prostate cancer patients. Recently, a predisposition locus, Hereditary Prostate Cancer 1 (HPC1), on chromosome 1 has been identified among families with PCa affected members (Smith et al 1996) and this was confirmed by another study (Cooney et al 1997). These rare genes appear to convey a high risk of PCa, but are believed to account for small proportion of cases except those with early onset (Carter et al 1993); the international and ethnic differences suggest that there may also be inherited factors which influence susceptibility to lifestyle and environmental exposures. Irvine et al (1995) presented data suggesting a possible association between CAG and GGC microsatellites of the androgen receptor (AR) gene and prostate cancer development. However, further data are still needed to establish the role of inherited susceptibility and predisposition in the PCa aetiology, especially in the age-group where it occurs most frequently.

On the contrary, the differences between populations of similar ethnic background such as the acquisition of higher risk by the Japanese immigrants to the USA compared to their peers in Japan (Haenzel and Kurihara 1968; Shimizu et al 1991; Parkin et al 1992), render the hypothesis of environmental origin of risk more appealing, with some valuable epidemiological observations that will be discussed here.

Diet: Among suspected risk factors, dietary fat intake was consistently linked to PCa. Ecologic studies showed strong positive association between PCa incidence (Kolonel et al 1981) or mortality rate (Blair and Fraumeni 1978; Howell 1974) with the percapita consumption of fat. Of thirteen case-control and eight prospective cohort studies reviewed by Kolonel (1996), positive associations with different relative risk estimates for fat and/or food sources of fat with PCa were noticed in all but two case-control and two cohort studies.

The odd findings of some studies can in part be explained by errors and bias in methodology which could have underestimated the true risk. Recall bias is a known shortcoming in case-control studies in general. Selection bias due to the low response rate among cases (51%) and the controls (39%) has affected the Canadian case-control study (Rohan et al 1995) with an inverse relation for saturated fat. Selection bias in the control group could occur with prostate cancer if clinically inapparent cancers were included in this group abolishing a real difference with the cases group in the exposure (Kolonel 1996). The use of hospital controls and the low average intake of fat among adults in Japan were suggested, by Kolonel (1996), as possible reasons for the negative findings in the study of Ohno et al (1988). Dietary information was limited (based on frequency of consumption only) in some of the

studies, including the two cohort studies that did not show any association with fat intake (Hirayama 1979; Hsing et al 1990) and only two studies (Whittemore et al 1995; Giovannucci et al 1993a) have been able to adjust for the confounding effect of total caloric intake. The inconsistent findings can also be attributed in part to the variation in the time at which exposure was measured. In this regard it was assumed that dietary fat intake may exert its effect at a late stage in disease development and positive results would therefore be anticipated from case-control studies and cohort studies with relatively short follow-up periods (Boyle et al 1995).

Considering some of these limitations, Key (1995) in her systematic review, has set criteria for choosing, whenever possible, results with least problems such as those adjusted for confounding, from studies with community controls and those for all and not a subset of cases. The summary relative risk (RR) she derived for highest versus lowest intake group was 1.34 for meat, 1.3 for dairy products, 1.31 for total fat and 1.54 for animal fat consumption.

Despite the methodological problems and that the excess risk due to fat is not so high (30-50%), researchers believe that the association of fat with PCa is quite consistent and the problem of inaccuracy in measuring dietary intake could underestimate the true relative risk (Key 1995; Kolonel 1996). The association is also biologically plausible and the effect of fat intake on prostate carcinogenesis is likely to be promoting, rather than initiating, by affecting prostaglandins synthesis and hormone production and metabolism (Rose 1986; Ross and Henderson 1994).

Other dietary elements investigated for its relation with PCa are vitamin A and its precursors but the results are equivocal suggesting that vitamin A and the *b*-carotene are unlikely to be important factors in PCa aetiology (Key 1995; Kolonel 1996).

Some of the discrepancy might, of course, be due to differences in the accuracy of intake measurement methods and failure to adjust for possible interaction between fat and other protective constituents of fruits and vegetables. Vitamin D deficiency has been suggested as a risk factor (Schwartz and Hulka 1990) but results were inconsistent. Corder et al (1993) found an inverse relationship between 1,25-dihydroxyvitamin D with PCa. Braun et al (1995) however, did not find any association with PCa for the prediagnostic serum vitamin D metabolites. In a recent trial men receiving supplementary α-tocopherol had a lower risk of prostate cancer than those who received the placebo; the age-adjusted relative risk was 0.66 (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994). Prostate cancer risk was found to be inversely related to the frequency of intake of beans lentils and peas among a cohort of Seventh Day Adventist men (Mills et al 1989). Zinc has been found to be lower in the cells and serum of small series of PCa patients compared to normal persons and patients with BPH (Habib et al 1979; Whelan et al 1983). It seems that many food constituents could be related to the risk of prostate cancer (including phytoestrogens and vegetable proteins) however, more data are required to confirm these findings (Kolonel 1996).

Sex hormones and sexual factors: Male sex hormones seem to have a role to play in PCa aetiology since they are vital for development and functions of the prostate (Rose 1986). This hypothesis is supported by the finding that men castrated before the age of forty were free from cancer at autopsy (Moore 1944). The hormonal influence on PCa has been assessed indirectly by studying sexual factors. Greater sexual drive (Steele et al 1971), fertility, having children (Armenian et al 1975) and higher number of marriages (La Vecchia et al 1993) were associated with

increased risk of PCa in these studies, but in a case-control study from Japan, marital status, fertility, ejaculation and masturbation were not linked to prostate cancer risk (Oishi et al 1990). The importance of these proxies will vary by geographical area and time period. Measuring serum hormonal level, Ahluwalia et al (1981) found that US patients had significantly higher levels of testosterone than US controls while among Nigerians it was significantly lower among cases than controls. Dihydrotestosterone serum level was similar in cases and controls (Ghanadian et al 1979; Ahluwalia et al 1981) or lower in cases than in controls (Nomura et al 1988). High testosterone: dihydro-testosterone ratio was associated with increased risk of PCa in one study (Ghanadian et al 1979) and not another (Meikle et al 1985). These inconsistent results may partly be due to selection bias and small sample size in some of the studies (Steele et al 1971; Ahluwalia et al 1981; Ghanadian et al 1979). Hormonal assessment can be affected by variation of serum testosterone level during the day (being highest in the early morning and declining thereafter), the difference in its clearance rate between cases and controls, and the divergence between tissue and serum concentration of androgens (Nomura and Kolonel 1991). Diet can affect serum hormone level (Hill et al 1979) and therefore adjustment for this confounding would be desirable. It is also that because blood was obtained after diagnosis in the case-control studies (Ahluwalia et al 1981; Ghanadian et al 1979) it is uncertain to what extent the presence of prostate cancer affected the hormone results.

Vasectomy: Vasectomy was studied for its association with the risk of PCa. Some cohort (Giovannucci et al 1993b; Giovannucci et al 1993c) as well as case-control studies (Mettlin et al 1990; Rosenberg et al 1990;) have reported very high relative risk (up to 5.3) of PCa among those with history of vasectomy compared to

non-vasectomized subjects. This contrasted with other studies of similar designs which reported insignificant results (Ross et al 1983; Honda et al 1988; Sidney et al 1991; John et al 1995). The last study in particular (John et al 1995) is a large population-based study with sound epidemiological methods applied in the selection of prostate cancer-free population controls (on PSA testing), assessment of non-response effect and adjustment for the effect of confounders including dietary intake of fat using the logistic regression analysis. The vasectomy relationship to the risk of PCa was discussed by the World Health Organization (WHO) experts who concluded that such a relationship is biologically and epidemiologically implausible (Skegg 1993).

Other factors: The relation between prostate cancer and benign prostatic hypertrophy has been studied but any causal link is still far from certainty and evaluation is difficult because of disclosure bias. Armenian et al (1974) reported greater risk of PCa among BPH patients than among age-matched controls. On the contrary, Greenwald et al (1974) found that BPH patients were not at increased risk for PCa. These two studies have been criticised for selection bias, and a plausible hypothesis given for the association is that BPH and PCa are two common conditions that share common risk factors (Nomura and Kolonel 1991).

Increased risk of PCa has been studied in relation to a number of occupations but findings were more consistent for farming (Boyle et al 1995). Employees of atomic energy plant who were exposed to radiation had a higher risk of PCa than the controls (Rooney et al 1993). Viral infections such as herpes simplex and cytomegalovirus, smoking and alcohol have also been studied for their involvement in

prostate cancer aetiology (Nomura and Kolonel 1991). Although these observations are not in themselves conclusive they highlight the need for further studies.

CHAPTER VI

TRENDS IN PCa REPORTED INCIDENCE AND MORTALITY IN SCOTLAND

1. INTRODUCTION

As in many other countries, reported registrations and deaths of prostate cancer in Scotland have increased over the past two decades. The disease is now the third most frequently reported cancer in men, following lung and large bowel cancers (Sharp et al 1993), and the second most common cause of cancer mortality (Registrar General Scotland 1994).

Many factors can influence trends of incidence and mortality and thus should be considered in interpretations. Among these factors are; changes in international classification of diseases (ICD) definition of cancer, coding practices and reporting efficiency. Among them also is inclusion of 'latent' carcinoma of the prostate, in situ cancer (in case of cervical cancer) or some benign or unspecified tumours as in brain and bladder cancer, in the incidence figures, and the effect of screening programmes (Muir et al 1994).

Cancer registration is expected to be specially incomplete at initial stages of the registry (Esteve et al 1994), and is likely to improve with time, driven by improvement in diagnosis, availability of medical services, and awareness of physicians and their readiness to report every case they diagnose (Doll and Peto 1981).

Improvement in registration of cases at the time of diagnosis of prostate cancer in Scotland has been shown using the trend in the proportion of cases discovered only from death certificates (Black et al 1993). Completeness of registration of PCa cases

has also been a subject of a number of studies in Europe (Robles et al 1988; Mattsson et al 1985; Brenner et al 1994), but to date there is no information on how much of the change in the disease incidence can be attributed to the improved reporting.

Incidence trend is liable to spurious change due to increased detection of cancers from the large pool of existing, but yet-to-be-diagnosed, cases (Muir et al 1994). Mortality trend could also be affected by this spurious change if it resulted in increased coding of prostate cancer as the cause of death (Whittemore 1994).

Analysis of time trends of the disease may not be conclusive of the exact influences of the trend, yet, in this regard, it remains as a useful hypothesis-generating method. This part of the thesis is a descriptive study of the trend in PCa incidence in Scotland over the past two decades (1971-1990). Use will be made of available routine statistical data on mortality and the number of TURP operations to assist interpretation of the trend phenomenon. The aim is to discuss and argue the possible contributions of different hypothesized trend components.

2. MATERIALS AND METHODS

2.1 Types and sources of data

2.1.1 Counts by 5-year age-group and year of diagnosis for registrations of all, and of all histologically verified cases of prostate cancers, registered with the SCR, diagnosed in Scotland between 1971 and 1990 were obtained from the Information and Statistics Division (ISD) of the National Health Service for Scotland (NHS).

2.1.2 Counts by 5-year age-group and year of death notification for Scottish males who died of prostate cancer between 1971 and 1990 and the mid-year estimates

of the Scottish male population in those years were obtained from annual report series of the Registrar General (Registrar General Scotland 1972-1991).

2.1.3 Counts by 10-year age-groups and year of operation for cases who have been admitted to hospital with benign prostatic hypertrophy (BPH) as the principal diagnosis on their Scottish Morbidity Records (SMR1) and treated with TURP were obtained from the ISD. The information was only available for the years 1975 to 1989.

2.2 Statistical methods

2.2.1 Calculation of rates

(a) The data were entered and saved on an EXCEL (version 5.0) spreadsheet file for analysis.

(b) Annual crude rates of incidence (registration), mortality and TURP were calculated for every 100,000 person-years using mid-year estimates for the Scottish male population.

(c) Annual age-specific rates of incidence, mortality and TURP were calculated using 5-year age-groups for the first two indicators and 10-year age-groups (<40, 40-49,..., 80+) for the third. These age-specific rates were then used to obtain the annual age-standardized[1] rates.

(d) Five-year average crude incidence and mortality rates per 100,000 person-years were calculated for the periods 1971-75, 1976-80, 1981-85 and 1986-90. These were derived by dividing the total number of cases or deaths from PCa reported in a five-year period by the total number of 10^5 person-years accumulated for the same period.

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[1] Rates were age-standardizd to the 1981 census for Scottish males.

(e) Similarly, five-year average age-specific incidence and mortality rates were derived for 10-year age-groups (<40,40-49,...,80+) using age-specific numbers of cases, deaths and person-years. These rates were applied to obtain the average age-standardized rates.

(f) The variance and 95 per cent confidence-limits of the average age-standardized rate were derived for each five-year period of observation. The variance was obtained using the formula described by Esteve et al (1994) in which,

the variance (V) *of "t"* $= \Sigma_x (w_x^2 / m_x^2) * k_x * 10^5$ where,

t is the period-specific age-standardized rate
w_x is the proportion of individuals in the x^{th} age-group in the standard population
m_x is the number of person-years accumulated in the x^{th} age-group of the population under study in the specified period
k_x is the number of cases or deaths reported in the x^{th} age-group of the population under study.

Under the assumption that the distribution of the standardized rate is approximately normal, the variance was used to build the 95 per cent confidence-limits of the rate as follows:

$$t \pm 1.96 \sqrt{v_t}$$

2.2.2 Changes in rates with time

Changes in age-adjusted incidence and mortality rates with time were assessed in two ways:

(a) Percent change from the base-period: This measures the total change in rates between the first five-year period (base-period) and the last one as a proportion of the first period rates.

So, percent change (% change) $= (R_y - R_b) / R_b * 100$ where,

R_b=rate in the 5-year base-period, R_y=rate in the last period.

This applies to crude, age-specific and age-standardised rates.

(b) t-test for the difference: The difference between any two standardized rates is statistically significant if it is ≥ 1.96 times its standard error ($\sqrt{(v_1 + v_2)}$). This must be applied in particular if their confidence intervals are not overlapped.

2.2.3 Incidence data quality

Incidence data quality were examined for change over time using the incidence-mortality ratio of age-standardized rates and the percentage of histologically verified cases among all registered prostate cancer cases.

3. RESULTS

Over 20 years from 1971 to 1990, absolute numbers of cases and rates of prostate cancer in Scotland saw a gradual increase (Table 6.1, Figure 6.1 & 6.2). Between the first and last five-year periods of the study, the absolute number and the crude rate averaged over 5 years increased by 84.4% and 87.8% respectively. After adjusting for the effect of ageing of the Scottish population the percent increase in the incidence rate was 57.8%. The standardized rate at each period was significantly higher than the preceding one (Table 6.1).

The mortality rate of PCa has also been rising but less rapidly (Figure 6.1 & 6.2). The average absolute number of deaths and the crude death rate of the disease rose by 48.5% and 50.9%, respectively, and the standardized rate rose by 23.3%. However, unlike the incidence rate, the difference in the standardized death rate between 1981-85 and 1986-90 was the only significant difference between two adjacent time periods (Table 6.2). Despite the overall increase in the death rate

however, it has also been noticed that over the last 3 years of the study period it was nearly stable (Figure 6.1 & 6.2).

The results show that the disease was rare below 50 years of age and rates are increasing with age reaching the maximum for men in their eighties (Tables 6.1 & 6.2).

The age-specific rates also have been increasing with time taking different patterns of proportional increases. Generally, the increase in the average incidence rate was higher among the lower age-groups. It increased from 55.4% for men in the fifties to its maximum of 66.7% among men in the sixties. It then declined in the higher age-groups reaching a minimum of 40% for men in their eighties (Table 6.1).

The average mortality rate increase ranges from 14.6% in men at the age of 80 years and above to 62.8% in men aged 50 to 59 years. In between however, the increase percentage was higher for men in the seventies (28.5%) than those in the sixties (18.1% - Table 6.2). Changes in rates in men below fifty years of age were disregarded because of the small numbers encountered.

Figures 6.3 and 6.4 show time trends in age-specific single year incidence and mortality rates on a log scale. The rates among men in the lowest age-group (50-59 years) are fluctuating but generally, there is an upward trend which is more prominent for incidence than the mortality rates.

Figure 6.5 shows the data of figure 6.2 with, in addition, variation in incidence-mortality rate ratio with time. Both age-standardized rates have been rising but the increase was higher in the incidence rate than in the mortality rate resulting in a slight improvement in the rate ratio from 1.6 in 1971 to 2.1 in 1990.

As a sign of improving accuracy of diagnosis figure 6.6 shows that the proportion of all registered cases that have been histologically verified rose very markedly from around 50% in 1971 to slightly over 84% in 1990.

At the same time as increases in incidence and mortality rates, the number of TURP operations performed as a treatment for patients with BPH also increased during the period from 1975 to 1989. Figure 6.7 shows the age-standardized TURP operation rate along with the incidence rate on a semi-log scale graph. It is evident that the upward time trend of TURP rate is much steeper. The age-standardized mortality rate of PCa is also shown to provide the reader with a log scale graph of the data shown in figure 6.2.

Table 6.1 Numbers (N), rates (R) and percentage change with time of prostate cancer cases registered at the Scottish Cancer Registry in 1971-1990

age-group		year of registration				71-90 % change
		1971-75	1976-80	1981-85	1986-90	
0-39	N	0	0	0	0	-
	R	0	0	0	0.1	-
40-49	N	3	3	4	5	-
	R	0.9	0.9	1.4	1.7	-
50-59	N	36	47	50	54	50.0
	R	13	16.5	18.1	20.2	55.4
60-69	N	189	232	253	303	60.3
	R	78.6	102.1	112.1	131	66.7
70-79	N	282	386	506	547	94.0
	R	248.2	300.6	360.2	400.9	61.5
80+	N	155	188	235	317	104.5
	R	502.6	604.3	632.5	704.2	40.1
all	N	666	855	1,048	1,228	84.4
	R	26.6	34.3	42.2	49.8	87.2
age-adjusted rate*		29.4	36.3	41.1	46.4	57.8
95-C.L. of rate		(28.4,30.4)	(35.2,37.4)	(40,42.2)	(45.2,47.5)	

* Rates were age-standardized to 1981 census of Scottish males by direct standardization.

Table 6.2 Numbers (N), rates (R) and percentage change with time of prostate cancer mortality reported in Scotland in 1971-1990

age-group		year of death				71-90 % change
		1971-75	1976-80	1981-85	1986-90	
0-39	N	0	0	0	1	-
	R	0.0	0.0	0.0	0.6	-
40-49	N	0	1	1	1	-
	R	0.1	0.5	0.4	0.5	-
50-59	N	12	18	20	19	58.3
	R	4.3	6.2	7.2	7.0	62.8
60-69	N	97	93	92	110	13.4
	R	40.3	41.1	40.9	47.6	18.1
70-79	N	172	194	241	265	54.1
	R	150.9	151.2	171.9	193.9	28.5
80+	N	122	117	142	204	67.2
	R	395.6	377.7	383.6	453.4	14.6
all	N	404	424	497	600	48.5
	R	16.1	17.0	20.0	24.3	50.9
age-adjusted rate*		18.0	18.1	19.4	22.2	23.3
95-C.L. of rate		(17.2,18.8)	(17.3,18.9)	(18.6,20.2)	(21.4,23)	

* Rates were age-standardized to 1981 census of Scottish males by direct standardization.

Figure 6.1 Crude registration (incidence) and mortality rates of prostate cancer in Scotland 1971–1990

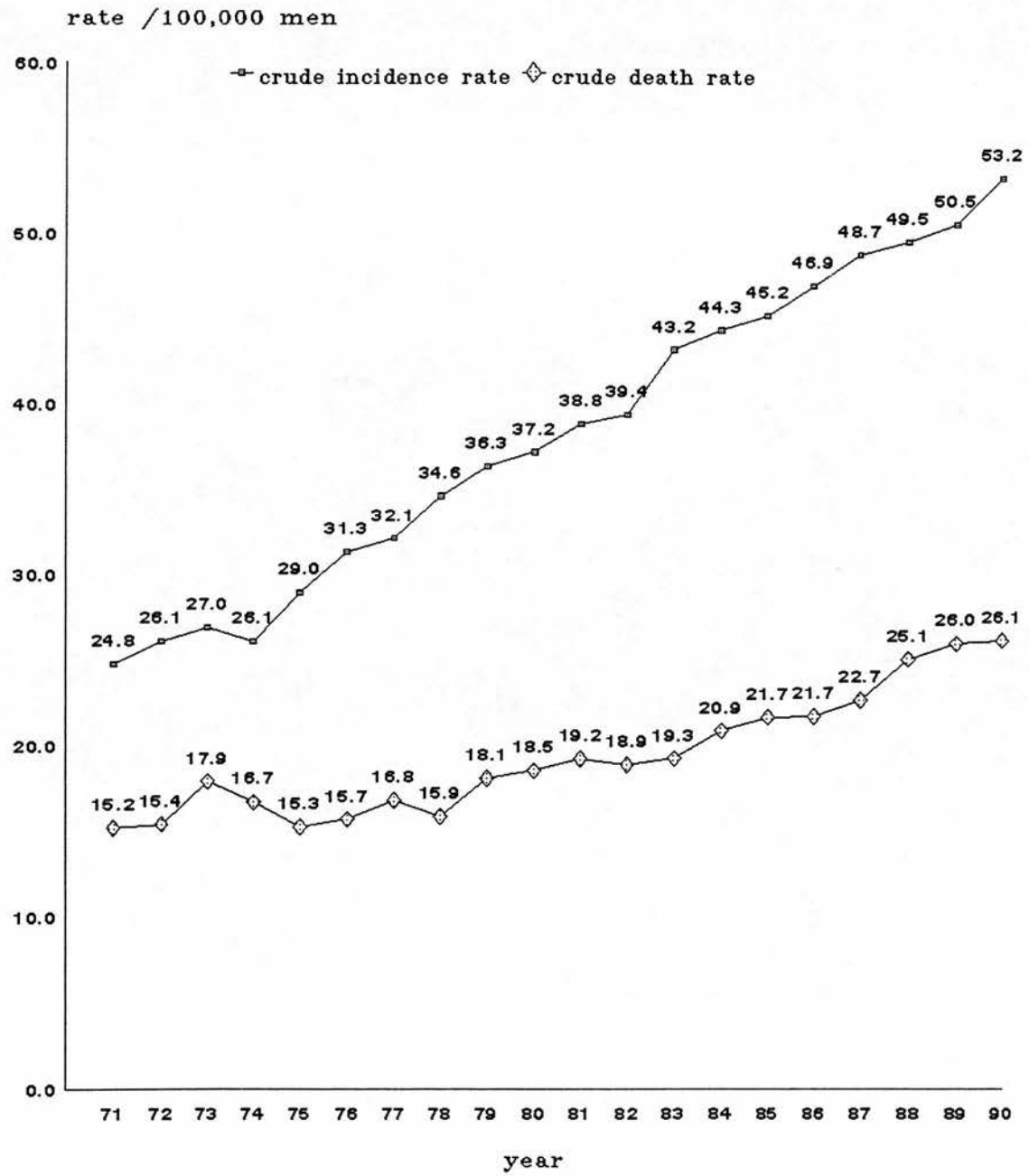
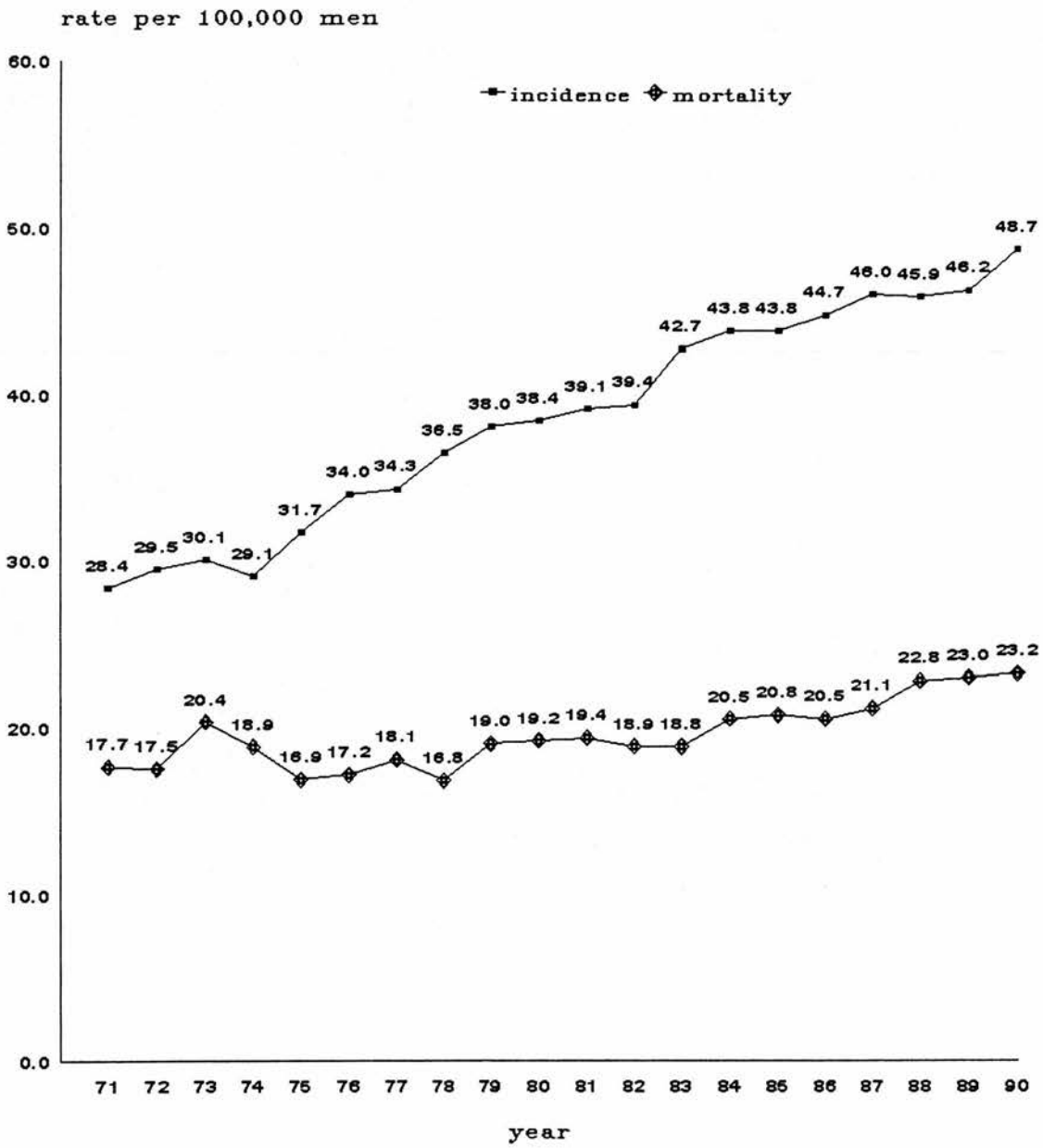


Figure 6.2 Age-standardized incidence and mortality rates of prostate cancer in Scotland 1971-1990



N.B. Rates are standardized to the 1981 census of Scottish male population

Figure 6.3 Age-specific incidence rate of prostate cancer in Scotland 1971-1990

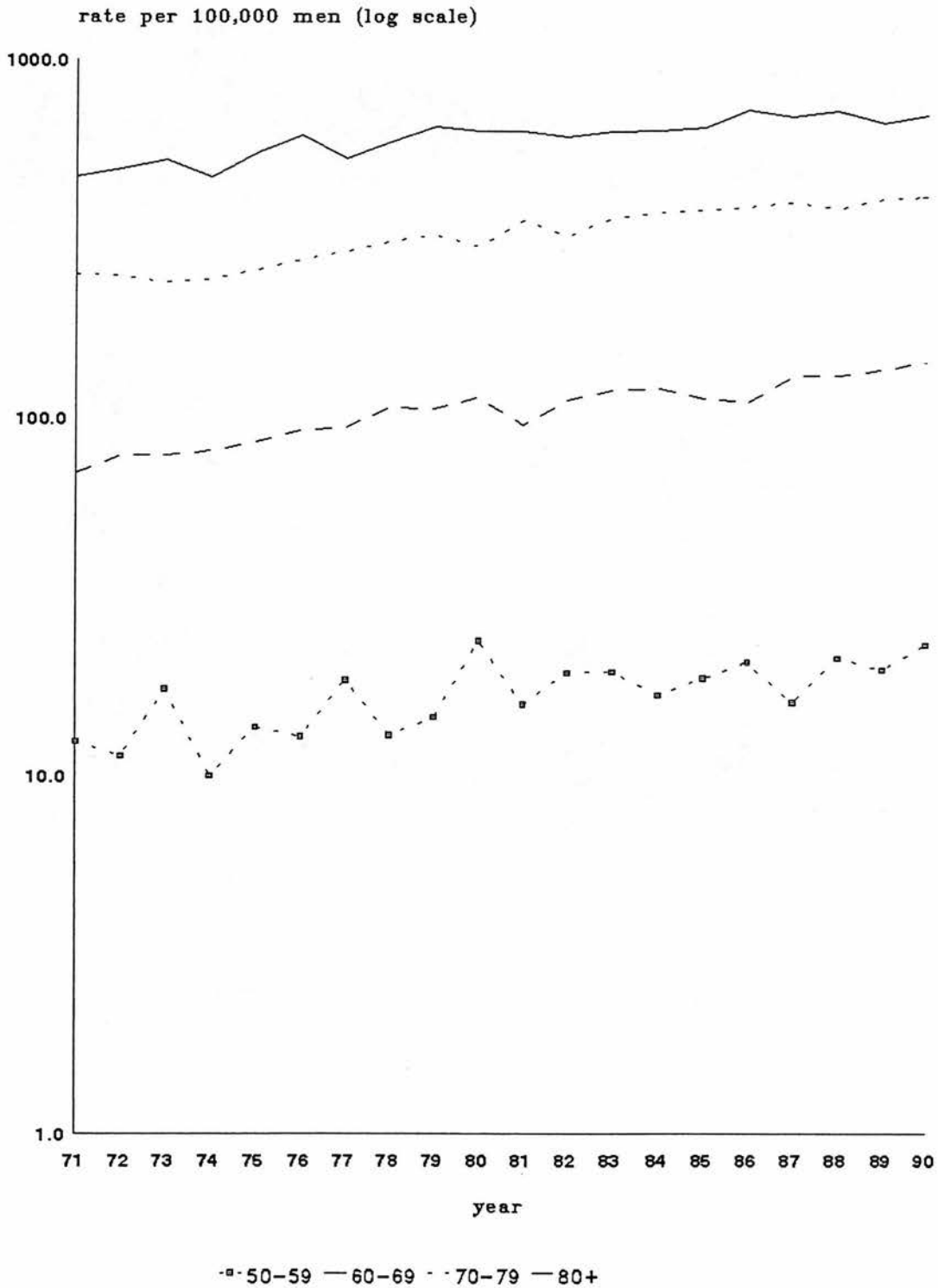


Figure 6.4 Age-specific mortality rate of prostate cancer in Scotland 1971-1990

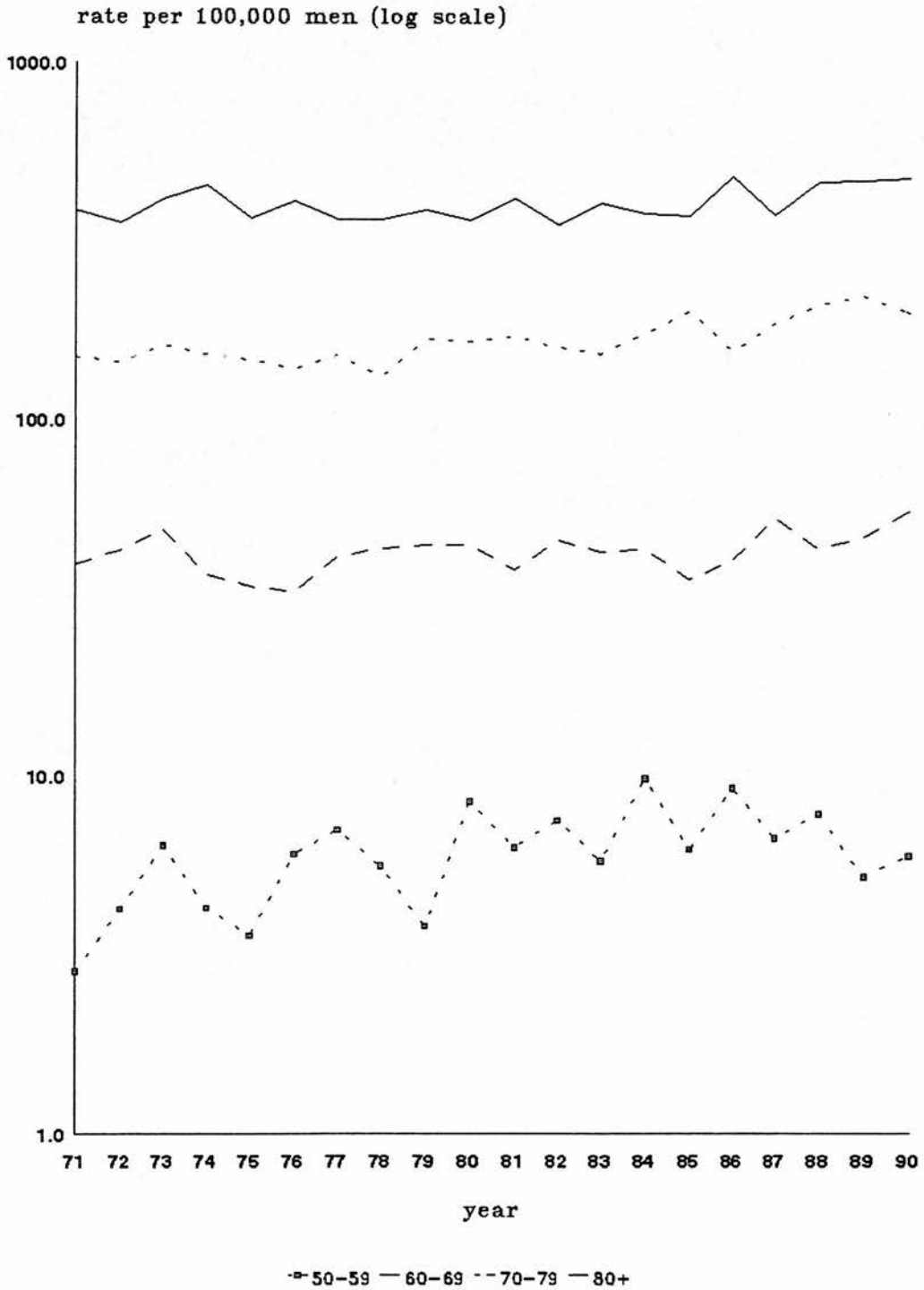
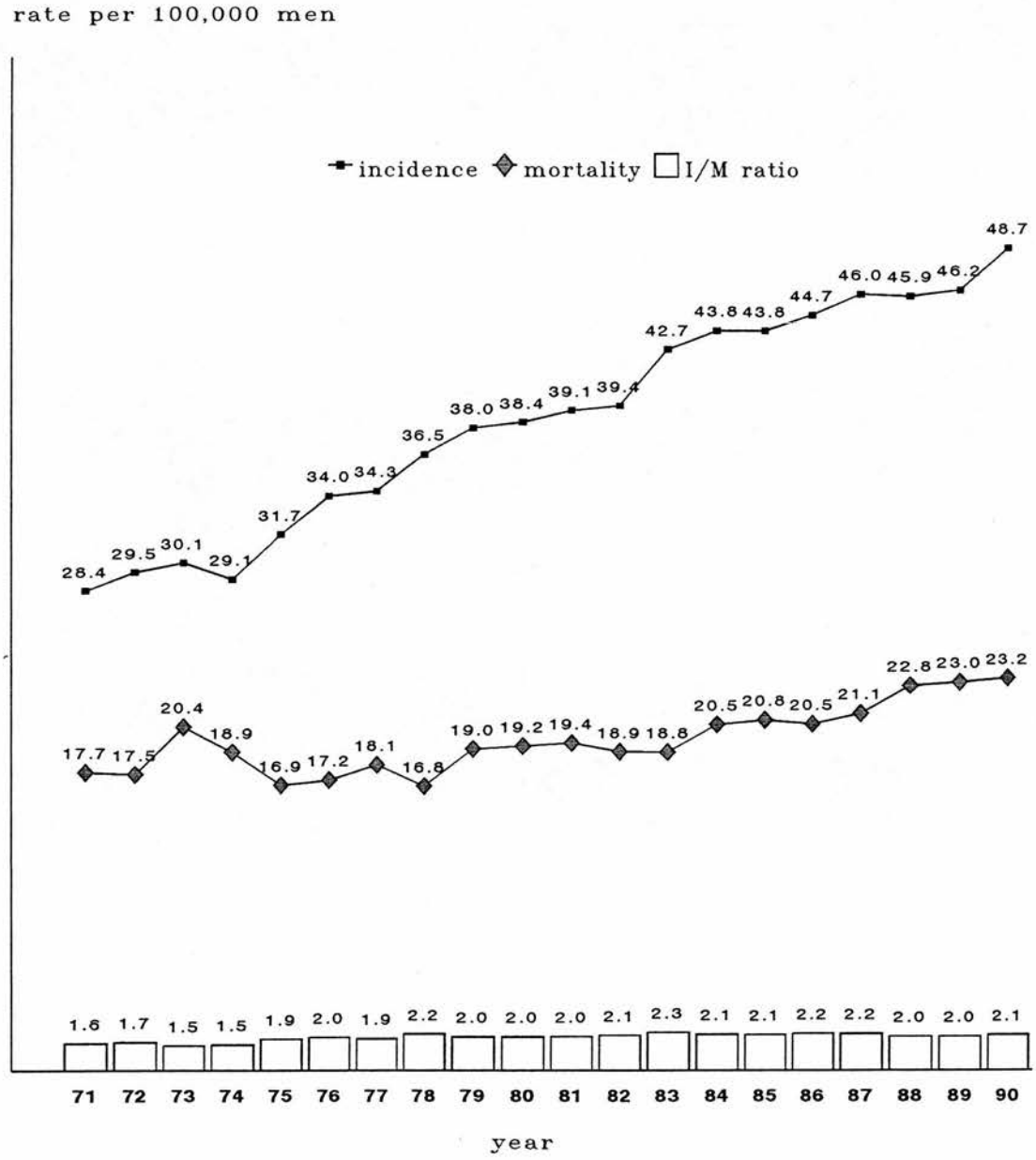


Figure 6.5 Age-standardized incidence and mortality rates and incidence:mortality ratio of prostate cancer in Scotland 1971-1990



N.B. Age was adjusted to the 1981 census of Scottish male population

Figure 6.6 Percentage of registered prostate cancer cases histologically verified in Scotland 1971-1990

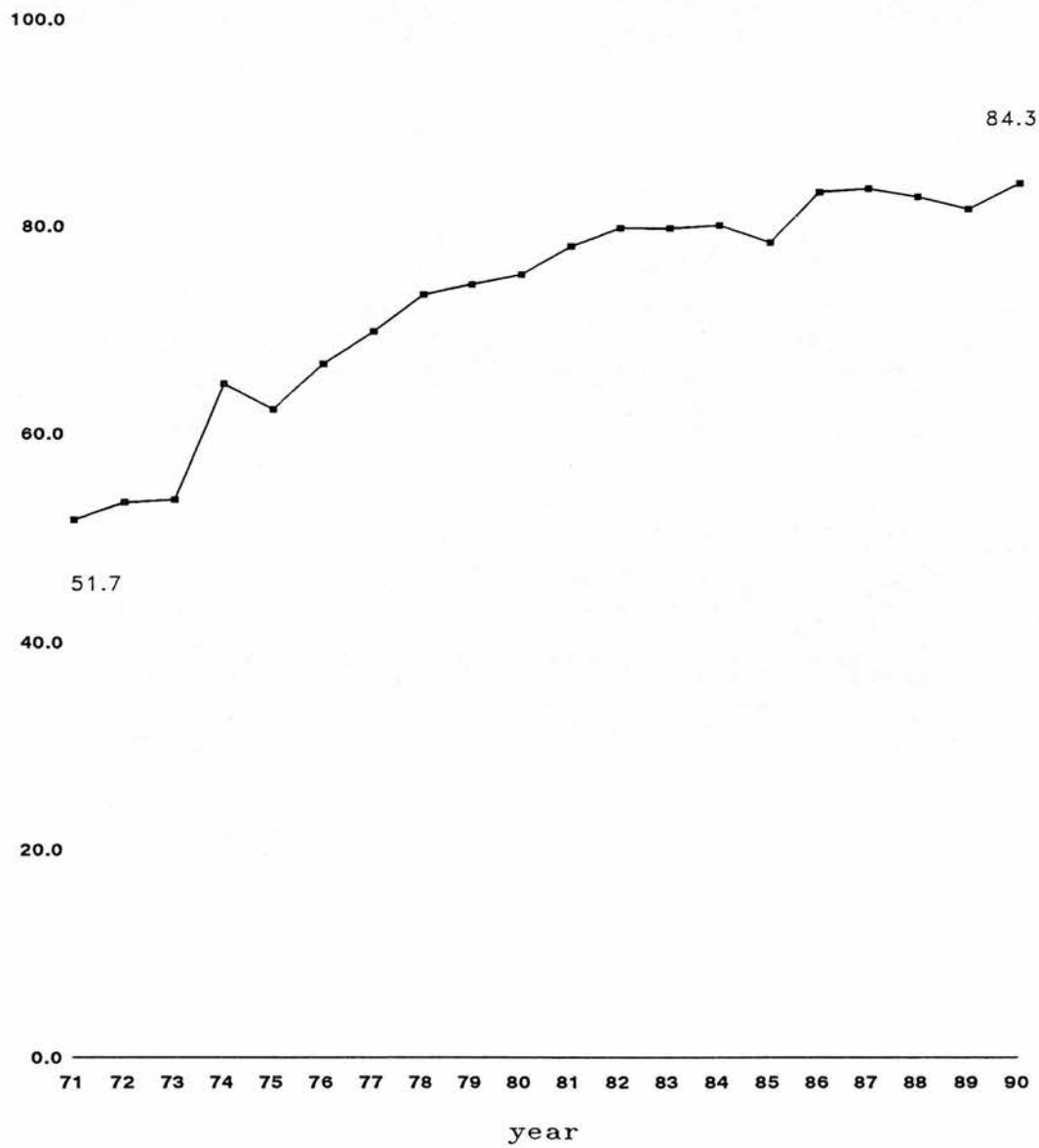
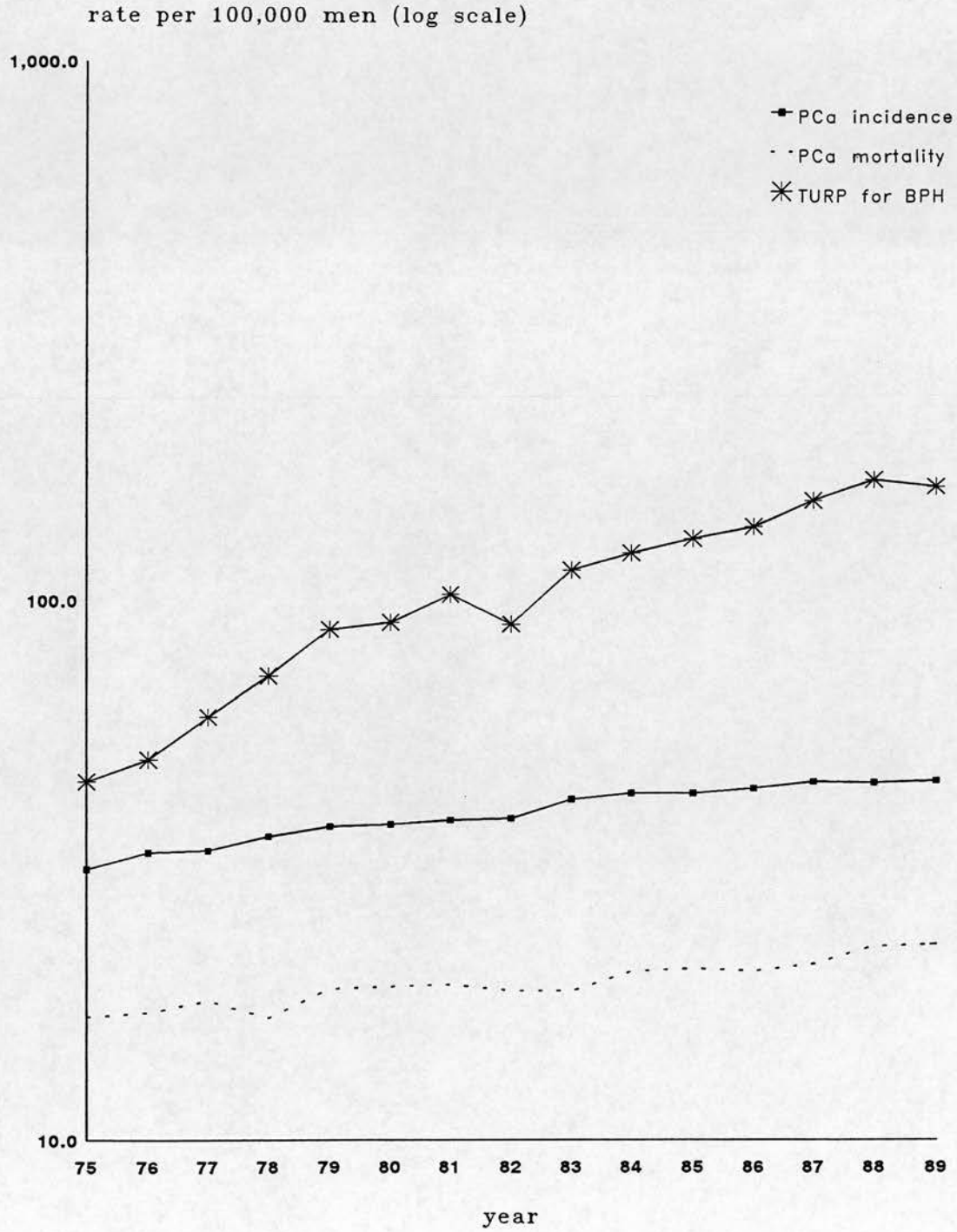


Figure 6.7 Age-standardized prostate cancer incidence and mortality and TURP operation rates in Scotland 1971-1990



N.B. Rates sre standardized to the 1981 census of Scottish male population

4. DISCUSSION

Prostate cancer now is the third most commonly diagnosed malignancy and the second cause of cancer deaths among men in Scotland. The disease has reached this level of priority as a public health problem in Scotland after more than two decades of a persistent rise that was more obvious for incidence than mortality. Between 1971-75 and 1986-90 the average crude and age-standardized incidence rates increased by 88 and 58 percent respectively. Corresponding increases in mortality rates are 51 and 23 percent.

Generally, many causes can be given for the rising trends in PCa incidence and mortality rates (Muir et al 1994), some of which are common in many places. However, in the light of the available routine data, the factors that could have influenced the PCa rising trends during the seventies and eighties in Scotland are:

(a) ageing of the population;

(b) improvement in incidence and mortality data quality;

(c) increased detection and reporting of incidental carcinoma as a result of increased performance of TURP for treating BPH cases;

(d) a true increase in the underlying risk of disease.

The same factors were suggested by Majeed and Burgess (1994) for the trends in England and Wales in the eighties. Age is an important determinant of prostate cancer. The data shows what is universally known about rarity of the disease before the age of fifty and its sharp increase afterwards reaching a maximum in the eighties. Scottish males now live longer than they did in the past; the life expectancy of a 50-year old man increased from 22 years in 1970-72 (Registrar General Scotland 1987) to 24.4 years in 1990 (Registrar General Scotland 1991). The absolute number of

men at the age of 70 years or more have increased from 241200 in 1970 to 293800 in 1990 (Registrar General Scotland 1991). The effect of ageing is well recognized by researchers in their attempts to explain the PCa increasing trends in other places (Whittemore 1994; Devesa et al 1995), and can easily be inferred from a comparison of the data from the difference in percentage increases of crude and age-standardized rates.

Improvement in incidence data quality may be inferred from the increase in the incidence-mortality (I/M) ratio, from 1.6 in 1971 to 2.1 in 1990, and the increase in the percentage of histologically verified cases, from 50 percent in 1971 to 84 percent in 1990 (Figure 6.5 & 6.6). Improvement in therapy can lead to an increasing trend in I/M ratio but in the absence of evidence to this improvement, the rise in the ratio showed indicates improvement in coverage or increased detection. An indication of improving coverage of PCa in Scotland was presented by Black et al (1993) using the percentage of cases registered from death certificate only (DCO cases). This percentage increased at the beginning of the study period but then started to decline. Thus, part of the rise in reported incidence could be due to this artefact.

The increasing percentage of histologically verified cases indicates improvement in the accuracy of diagnosing PCa. However, as shown in the Scottish study (Brewster et al 1994) histological verification status is liable to two coding errors: of assigning histologically verified cases to the not-histologically-verified category and vice-versa with the first type more common than the second.

According to the same study, the reported incidence is subject to error of coding the anatomical site of the tumour by relocating cancers suspected to be of other organs to the prostate and vice-versa (Brewster et al 1994). Therefore, assessing the

influence of improving diagnostic quality on the reported incidence trends of PCa requires the knowledge of the amount and direction of these coding errors. To some extent, their influence is diluted by their bi-directional nature.

As far as incidental PCa is concerned the data strongly suggest that increased detection of these cases by examination of prostatic tissue removed by TURP operation for treating BPH was a major component of the trend of PCa incidence in Scotland during the late seventies and the eighties. The frequency of this surgery showed a dramatic rise (Figure 6.7), and according to Duncan and Garraway (1993), dominated prostatic operations (99%) for BPH in Scotland by the end of that period. It is known that around 14 percent of these surgeries results in the incidental finding of malignant foci (Alexander and Boyle 1995). This could fall to 4% or rise to 21% depending on variation in patients' characteristics and the protocols for pathological examination of prostatic tissue where any change from routine sampling to step-sectioning technique would increase the detection of incidental PCa even if the number of TURPs did not change. Discussions with pathologists in various regions of Scotland indicate that there has not been any change in the prostatic tissue examination technique during the study period (personal communications) and therefore any increase in these cases is likely to have happened just because of the increasing trend in TURP rate. Indirect evidence of the increased detection of the incidental PCa is the improved survival of the disease in Scotland during the period 1968-72 to 1982-87 (Black et al 1993).

Screening for PCa using prostate specific antigen (PSA) test contributed to the rising incidence trend in the US in the late eighties (Potosky et al 1995) but to the

best of the investigator's knowledge such large scale programmes have still not been started in Scotland.

In contrast with the Scottish Cancer (incidence) Registry, the mortality register in Scotland was established very much earlier, before the turn of this century (Office of Population Censuses and Surveys 1979), and therefore, mortality data of the last two decades would be less affected by improvement of coverage than the incidence data; it may, however, be influenced by improvement of accuracy of diagnosis. The latter has been postulated by La Vecchia et al (1992) in their report on the trends of prostate cancer mortality in Europe. However, an over 50 percent increase in the mortality rate cannot be explained entirely by improvement in coding PCa on the death certificate and is likely to indicate an increase of clinically progressive disease.

Despite the limitations of this study design, it has presented evidence and generated some hypotheses about the possible factors that have influenced PCa incidence and mortality trends in Scotland. It has also provided an estimate of the change in these two frequency measures using a simple method, the total percentage increase over the base-year rate, which is commonly used in trend analysis (Whittemore 1994; Devesa et al 1995).

An increase in autopsy rate may cause an artefactual rise in the reported incidence if incidentally found cases from this procedure were included in the statistics. In Scotland, cases detected at autopsy are included in the incidence statistics (Parkin et al 1992) but the autopsy rates in Scotland were low (Cameron et al 1977), although recent data are not available.

In conclusion, the rise in the reported incidence rate of PCa in Scotland during 1971-1990 comprises an artefactual component mainly due to improvement in

reporting and increased detection of TURP-detected incidental cancers, and a true component due to increased reporting of progressive cases which in turn could mean an increase in exposure to PCa risk factors.

CHAPTER VII

TREND IN ESTIMATED COMPLETENESS OF PROSTATE CANCER REGISTRATION IN SCOTLAND

1. INTRODUCTION

As with any registry, the Scottish Cancer Registry **(SCR)** provides data which are useful in determining site-specific incidence rates and studying trends in incidence over time and space. However, such data are difficult to interpret without evaluating the numerator's completeness and accuracy; problems are quite common in the cancer registration process. The aim of this study, is to examine completeness of reporting of prostate cancer at the SCR, in order to estimate how much of the increase in its reported incidence can be explained by changes in completeness.

So far in the United Kingdom, and Scotland in particular, evidence on the completeness of registration in prostate cancer are lacking. Some studies have looked into completeness of cancer registration in general (Haddow 1968; Alderson 1971; Faulkner et al 1967; Benn et al 1982; West 1973; Freedman 1982), while others were site-specific for leukaemia (Alexander et al, 1989) and stomach cancer (Donan, 1982). Faulkner et al (1967) have reported on site-specific completeness rates, but apart from the small number of prostate cancer cases in the study sample (23), the results are irrelevant to the present period.

Inferences from these studies about completeness of prostate cancer registration in Scotland are difficult to make because of variability of completeness between different registries, for different cancer sites and over time. An opportunity to assess completeness of PCa completeness is available, using the Scottish Morbidity Records (SMR1), as an alternative source of identification of PCa cases.

The SMR1 data base is intended to gather and store information on in-patient discharges for non-psychiatric non-obstetric general morbidity in hospitals all over Scotland. The information is received at ISD on special forms (SMR1), nowadays on magnetic tapes, with six entries for diagnoses, allowing for cancer to appear even if it is not the principal disease in the admission. In comparison with patients' clinical case notes, Lockwood (1971) has shown that SMR1 is highly accurate for transcription of patients' identifying information (99.68%), administrative information (95.75%), principal diagnosis (93.76%) and principal operation (89.72%).

There are other sources which can be used in assessment of completeness of cancer registries. Death records have been commonly used in these kind of studies (Haddow 1968; Alderson 1971; Faulkner et al 1967; Freedman 1982 and Mattsson et al 1985), but their main disadvantage is poor coverage for cancers with low case-fatality (Goldberg, et al 1980). Based on an 1.9 incidence : mortality ratio (Wilson 1987), at least 50% of diagnosed PCa cases will not be found on death records. The chances of PCa appearing on the death certificate should be slim if it has not contributed to the death; this may apply to as many as 50% of patients with clinically-detectable cancer who die with the disease rather than of it (Schroeder 1995).

Pathology laboratory records are another alternative source but will only cover those cases which are confirmed by histology or cytology. Therefore, more than 15 per cent of cases registered without histological verification (Black et al 1993) will be missing on these records.

With all the advantages of the SMR1 scheme over other sources and despite its positive aspects shown by Lockwood, its coverage for PCa cases remains uncertain, and it is possible that a number of cases would be missed by both the SMR1 scheme

and the SCR. Information on counts of these cases are crucial for determination of completeness of PCa registration, but direct ascertainment is only possible by carrying out an independent intensive survey, which is the most definitive but very expensive approach (Goldberg et al, 1980).

An *estimate* of the count of these cases can be obtained using one of the estimation methods. Goldberg et al (1980) have discussed the 'historical data' method which is a rough method, and in which the expected number of cases is calculated using incidence or prevalence rates of a demographically similar population.

A more precise approach uses an estimate derived by what is known as the "Capture-recapture" method. This method, the theory of which was described by Bishop et al (1975), was first used to count abundance of animal populations, but then became a very popular method of estimation of populations in many other scientific disciplines including study of cancer registration completeness (Robles et al 1988; Brenner et al 1994).

The intention in this study is to implement this statistical technique which will yield a maximum likelihood estimate of the total number of prostate cancer cases that would have been diagnosed during the study period. It requires the assumption that reporting of cases to the SMR1 scheme and to the SCR are two *independent* processes. This pre-condition may not be true in the day-to-day practice but is necessary for the calculation of our estimate. Violation of the rule of independence of the two sources would, inevitably, lead to underestimation of the true number of all PCa cases, and thus overestimation of the completeness of both sources, which will be considered in interpreting the findings.

2. SUBJECTS AND METHODS

2.1 Design and period of the study

This is a retrospective record linkage study of all cases of prostate cancer diagnosed in Scotland who were either registered at the SCR, or have a record on the Scottish Morbidity Record (SMR1) scheme, or both. The two sets (cancer registry and SMR1) will be compared with each other and assessed for their completeness of ascertainment of prostate cancer cases. Under the assumption of their independence capture-recapture methods will be used to estimate the total number of PCa cases diagnosed in Scotland. Initially, the study was meant to cover the period from 1981 to 1990 but, following validation and preliminary analysis, the year 1981 was omitted.

2.2 Study subjects

The Information and Statistics Division (ISD) of the National Health Service for Scotland (NHS) has constructed a linked data-base file in which patient's Scottish Morbidity Records (SMR1) for his admission to one of the hospitals in Scotland, his SCR records (SMR6) and his death record, available from the General Register Office (GRO), are linked together by a probability matching method (Kendrick and Clark 1993).

The SMR1 and SMR6 are two data sources with the Scottish Morbidity notification systems. The SMR1 is used to notify any morbidity, except those of psychiatric or gynaeco-obstetric nature, that leads to hospital admission. It is therefore an event-based system with an SMR1 record issued for every admission even those due to the same morbidity. This record contains information related to the admission diagnoses and the procedures carried out for the patient.

The SMR6 is the cancer registry notification system and an SMR6 record should be created only once for any one site, at the ISD, unless the system failed to identify a duplicate or a new primary was diagnosed (e.g. for breast cancer). It contains information on cancer site, morphology of the tumour, date treatment commenced (diagnosis or the anniversary date) and date of death (if it occurred).

At ISD, all the SMR1 and the SMR6 records since 1981 that belong to the same individual are linked together. For the purpose of this study, for each patient, only the first SMR1 record with prostate cancer diagnosis in the period 1981-1990 and , if applicable, only one SCR record for PCa during the same period were selected. Selection of the first SMR1 record was meant to include the record that is most likely to be the diagnostic one.

From this linked data base a file was prepared by ISD, by selecting any patient who met **ONE OR MORE** of the following criteria:

1. Has a record at SCR for prostate cancer with a date of treatment commencement (anniversary or diagnosis date) between 1981 and 1990 inclusive.
2. Has an SMR1 record mentioning prostate cancer as one diagnosis for a date of admission in the period 1981-1990.
3. Has died in the same period (1981-1990) and had prostate cancer diagnosis on his death certificate as direct, underlying or associated cause of death.

2.3 Data validation

The data set was checked for the following aspects:

2.3.1 Total number of PCa cases with an SMR6 record

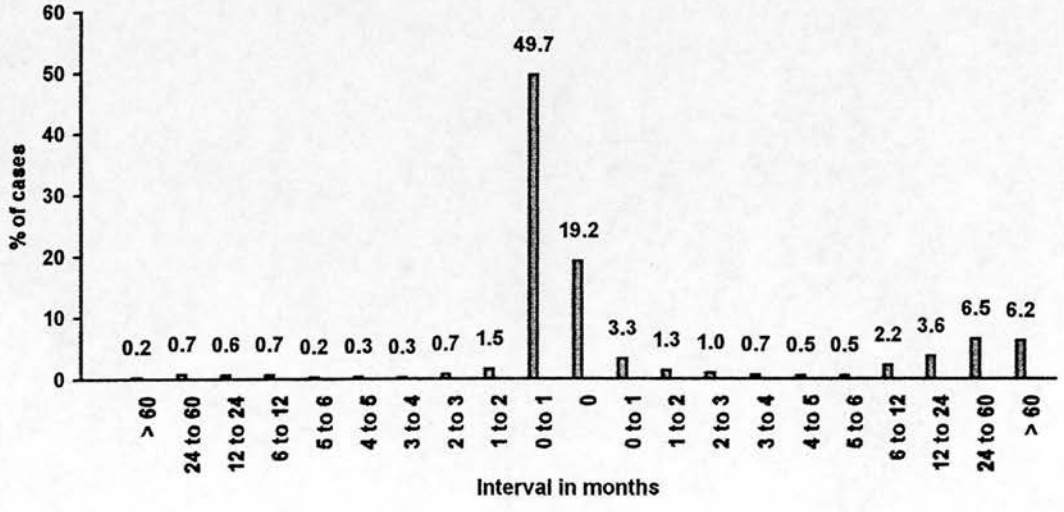
This was checked against published figures of PCa registrations. For details see section 1 in appendix A.

2.3.2 Consistency in SMR6 and SMR1 dates of diagnosis and admission

Following identification of errors of section 2.3.1 above, ISD supplied modified data which were checked further for discrepancy in diagnosis and admission dates on both SCR and SMR1 records of the same patient, with the aim of ensuring consistency between the two linked records. Examination of the time interval between the two dates showed that cases with different dates had a variation of up to 10 years with an average of about 0.7 years (s.d.= 2.3). However, out of 10396 cases with two linked records 2001 (19.2%) have two identical dates. Including those, a total of 7980 (76.8%) had dates within ±3 months, and for the vast majority of cases (8539 or 82.1%) dates lie within ±12 months difference (see Figure 7.1 below).

For these reasons, cases have been classified so that those who have a date difference equal to or less than ±12 months were considered "consistent matches" and interpreted as referring to the same episode, and those whose dates were more than ±12 months apart were considered "inconsistent matches".

Figure 7.1 Percentage distribution of PCa cases by admission-treatment interval



2.3.3 Completeness of SCR relative to PCa cases on SMR1 by time

A preliminary analysis was conducted to estimate completeness of PCa registration (SCR) relative to cases on the SMR1 scheme. The capture-recapture method estimate of SCR completeness by year was derived. These findings led to identification of a new problem. Cases registered prior to but treated for recurrence or related conditions during the study period had SMR1 records without SMR6 ones. This was rectified at ISD by cross-checking SMR1s against earlier SMR6s. In the analysis reported here, SMR1 records corresponding to cancer registrations before 1981 have been excluded. The results from the preliminary analysis and its commentary are shown in section 2 of appendix A. 1981 was excluded from the present study at this stage since corresponding adjustments could not be made.

2.4 Data preparation and coding

2.4.1 Study data set

The following steps were performed in sequence to obtain the best possible set of matched records with one or both SMR1 and SMR6 in 1982-90:

(a) A final data set was supplied by ISD containing all prostate cancer cases with SMR1 records during the period 1981-1990 (11458 cases) and their linked SMR6 record, if there was any, dated before, during or after that period (10409).

(b) The data were checked for missing information, and date of birth was found to be missing in 6 cases, SMR6 date (date treatment commenced) was missing in 13, and health board of residence code was not available in 57 cases.

(c) Coded age at registration (SMR6) and admission (SMR1) was compared with the calculated one and the former was corrected only for cases where the century was not

accounted for or if the absolute difference between the calculated and the original age was greater than one year.

(d) Any SMR1 was set to missing if it was dated before 1981 or more than one year after the matched SMR6 record. As a result, a total of 1711 cases have been set to missing. In 12 of these cases, full dates were not available and the calendar years of their SMR6 and SMR1 records differed by 2 or more. In another case the difference was more than one year on the basis of age at registration. Setting cases to missing on SMR1 removes SMR1s that cannot be diagnostic.

(e) SMR6 records were then set to missing if the date of registration was before 1981. At this point, 1048 men had their records set to missing for both SMR6 and SMR1. After this, a total of 10410 cases were left for study in this data set.

(f) A second data set incorporating all cases with an SMR6 record but no SMR1 record (1442) that have been registered during 1981-1990 was derived from the old master set provided by the ISD. Age was calculated on the basis of years of birth and registration because full date of birth has not been supplied for the cases in this data set. Original age was corrected if the difference from the calculated one was more than one year. Accordingly 3 cases only have their age modified.

(g) The second data set was then appended to the first set to form the final study data set comprising 11852 cases and after exclusion of records of 1981 and 1991 and above there were 11169 cases left between 1982 and 1990 for the analysis.

2.4.2 Variable coding

The data for analysis were derived from the three schemes (SMR1, SCR and GRO death records), and contain individual information on dates of events (admission, diagnosis, operation and death), patient's age at event, health board of

residence at event, hospital of event, diagnosis at event, histological verification of PCa cases, death certified only (DCO) cases, causes of death and year of birth.

A new variable was created indicating the source of the fact of PCa information, and also new ones for the year of diagnosis, patient's age at diagnosis and region of diagnosis, to overcome problems of discrepancy when these were calculated from SMR1 and SCR data. These new variables were created as follows:

(a) Source of cases: Cases were coded '1' if they have an SMR1 but no SCR record, '2' if they have an SCR record but no SMR1 or have both records but were inconsistent matches (dates differ by more than 12 months) and '3' if they have both SMR1 and SCR records and were consistent matches (dates are the same or differ within 12 months). There were only 368 cases on the Registrar General's death records who died with prostate cancer between 1982-1990 and have neither SMR1 nor SCR record. These cases were not considered further in this study.

(b) Year of diagnosis: For cases with source code '1', year of diagnosis was taken from year of admission and for those with source code '2' from year treatment commenced. If source code was '3' and the date of admission was equal to the date treatment commenced , the year of diagnosis was equated to year of treatment. If the two dates were not equal, the average interval between the two dates (SMR1 date - SCR date) for consistent matches (cases with source code '3') was calculated and subtracted from the SMR1 date. If the two years were then equal, the common (SCR) year was chosen, but if not, one of the two years was chosen at random (a command file was created on SPSS to give a random digit between 0 and 1. The SCR year then was chosen if the random digit was >0.5-1.0, and SMR1 year value was chosen if the random digit was 0.0-0.5).

(c) Age-group at diagnosis: Age-group at admission on SMR1 and at treatment on SCR were reclassified into nine groups beginning with 35-49 years followed by 5-year age-groups until 85 and above group. The value of age-group at diagnosis was equated to the value of age-group at admission for cases with source code '1' and to that of age-group at treatment for cases with source code '2'. For cases on source code '3', the SCR value was chosen if it is equal with SMR1 value. If the two were not equal, patient's ages at treatment and at admission were calculated using the year of birth, with the day and month of birth were fixed at 30th of June for all cases[1]. The patient's age at admission was then adjusted, by subtracting the average number of days between the date of admission on SMR1 and the date of treatment on SCR (as in b above) and compared with the age at treatment for any difference between them. Age at diagnosis was equal to the value of age at treatment plus a random digit of the difference. The resulted age at diagnosis was re-coded into the nine age-groups as above.

(d) Region of cancer registry: There are five regions of cancer registration in Scotland representing the main hospital boards in Inverness (north), Aberdeen (north-east), Dundee (east), Lothian (south-east) and greater Glasgow(west). Region variables were created on SMR1 and SCR (**'region1'** and **'region6'**) by re-coding the health board of residence at admission or treatment. A new common variable called **'region'** was created so that for cases with source code '1' the values for the common **'region'** variable were taken from **'region1'** and for those with source code '2' from **'region6'**.

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[1] Full date of birth was not supplied with the data for reasons of confidentiality.

For cases with source code '3', the value of **'region'** was equated to the value of **'region6'** if the latter was equal to **'region1'** value. But, if **'region1'** and **'region6'** values were not equal, then the percentage distributions of **'region1'** and **'region6'**, among cases in source code '3' with equal values of the two variables, were used to calculate a probability for the region6 region that is equal to number of cases in that region divided by the number of cases in that region and region1 region combined. A random number between 0 and 1 was generated by the analysis software and compared with the **'region6'** probability. If the created random probability was smaller than the **'region6'** probability, **'region'** value was made equal to the **'region6'** value, otherwise it was equal to the **'region1'** value. Thus inconsistent allocations of region by the two sources were randomly assigned to one choice with probability proportional to number of registrations from each region.

2.5 Statistical methods

2.5.1 Estimation of completeness of prostate cancer registration by capture-recapture method

The counts of PCa cases can be displayed diagrammatically as follows:

		SCR for PCa		
		yes	no	
SMR1	yes	a	b	(n2)
for PCa	no	c	d?	(m2)?
		(n1)	(m1)?	N?

where,

a = number of PCa cases on SMR1 and SCR schemes,

b = number of PCa cases on SMR1 only,

c = number of PCa cases on SCR only and

N = total number of diagnosed PCa cases.

? = unknown quantity

From this cross-classification, completeness of SCR and SMR1, relative to each other, for PCa (relative completeness) is a/n2 and a/n1 respectively. Total completeness of PCa registration on each scheme is (a+b)/N and (a+c)/N respectively, and the overall completeness is (a+b+c)/N.

The same formulae can be applied to determine completeness by patients' age-group, year of diagnosis and health board of residence. However, given that neither SMR1 nor SCR is a complete list of PCa cases, the total number of cases 'N' is not known due to unknown cases in cell 'd'. The solution to this is to replace the common dominator 'N' with an estimate (NE) that will be obtained by the application of capture-recapture method as shown below.

(a) The technique: As the name implies, in classical applications, a sample or a list of subjects from a target population is obtained and those captured are identified i.e. tagged, but then returned to the source population. Another sample or list is obtained and the subjects are divided into those who have been identified, or tagged in the preceding sample, and those who have not. The sampling can be carried out any number of times but the simplest form and the easiest to calculate is two-sample capture-recapture technique. From the number of subjects in each sample and of those recaptured the size of the target population is estimated according to the underlying theory and its formulae as it is described in the following section.

(b) The theory and the formulae: The theory of the two-sample method is that described by Bishop et al (1975) for estimation of the size of closed population using

an incomplete 2x2 table approach. A very crucial assumption in this approach is the independence between the two samples or lists. Under this assumption of independence and from the cross-classification of SMR1 and SCR above,

E(a) = n1 * n2 / N. For the maximum likelihood estimate (MLE) of N we equate 'a' with its expected value E(a) so that, a = n1 * n2 / NE and thus,

the estimator of N (NE) = n1 * n2 / a Where,

n1 = observed number of subjects in first sample or list

n2 = observed number of subjects in second sample or list, and

a = number of tagged (re-captured) subject in second sample.

Where small cell counts are encountered, Wittes and her colleagues (1974) have found it necessary to make a slight adjustment to this formula so that

NE = [(n1 + 1) * (n2 + 1) / (a + 1)] -1.

The variance of NE = $(n1 + 1) * (n2 + 1) * b * c / \{(a + 1)^2 * (a + 2)\}$.

(c) Application: In this study the modified formulae were applied to estimate the total number of prostate cancer cases that would have been diagnosed in Scotland during the study period (1982-1990). The SPSS software package was used to create three tabular form of files each aggregated by one of the classification variables (year of diagnosis, age-group at diagnosis and region of cancer registration). In each file the estimator of the total PCa cases (NE), and its variance were calculated by the modified formulae. The 95% confidence limits (CL) of the estimator, and SCR completeness for prostate cancer registration and its confidence limits were calculated as follows:

SCR completeness for PCa registration = n1 / NE * 100

lower 95% CL of NE (loNE) = NE - 1.96 standard deviation (NE)

upper 95% CL of Ne (upNE) = NE + 1.96 standard deviation (NE)

lower 95% CL of SCR completeness = n1 / upNE * 100

upper 95% CL of SCR completeness = n1 / loNE * 100.

Completeness was estimated for total period and by each of, year of diagnosis, patient's age at diagnosis and the region of cancer registry to examine its variability over time, age and place.

2.5.2 Calculation of observed and estimated incidence of prostate cancer

From the master data set a file aggregated by year of diagnosis (1982-1990) and age-group at diagnosis was created containing fields for the aggregated variables and the number of PCa cases corresponding to a, b, c, n1 and n2 variables in each age-group in each year. The year of diagnosis was re-coded into three 3-year periods; 1982-1984, 1985-1987 and 1988-1990, and the counts of cases in a, b, c, n1 and n2 in each period was their sum over years of that period. Mid-year population estimates of number of Scottish males in the same age-groups and periods, and the standard world population counts for males in the same age-groups (Muir et al 1987) were imported to SPSS and combined with PCa data to permit calculation of age-specific and age-standardized rates. The estimator (NE), its variance and 95% confidence limits, and SCR completeness were derived by the previous equations.

The observed age- and time-specific incidence of prostate cancer (cases registered at SCR) was calculated for every 100,000 of Scottish males according to the following equation:

age-specific incidence rate $(ASPIR)_{ij} = (n1)_{ij} / p_{ij} * 100,000$ where

$(n1)_{ij}$ = observed number of PCa cases on SCR in i^{th} age-group (i=1,..9) and j^{th} period (j=1,2,3), and

p_{ij} = mid-year estimate of male population in i^{th} age-group and j^{th} period.

The estimated age-specific incidence rate was calculated by replacing NE_{ij} (estimated number of cases) for $(n1)_{ij}$ in the above equation.

Observed and estimated crude rates in each period were calculated as follows:

observed crude incidence rate = $(\Sigma_i (n1)_{ij}) / P_j * 100{,}000$

estimated crude incidence rate = $(\Sigma_i NE_{ij}) / P_j * 100{,}000$ where,

P_j is the mid-year estimate of the total number of male population in Scotland aged 0 and above during the j^{th} period.

To adjust for the effect of changes in age structure of the population on interpretation of the trend in PCa incidence rate, age-standardized rates were obtained by applying the direct-standardization method (Armitage and Berry, 1987) and using the world standard population (Muir et al 1987) as a standard. The standardized rates were derived for each period:

observed age-standardized rate $(OASIR)_j = \Sigma_i \{(n1)_{ij} / p_{ij}\} * p_{iw} / P_w$

estimated age-standardized rate $(EASIR)_j = \Sigma_i (NE_{ij} / p_{ij}) * p_{iw} / P_w$ where,

p_{iw} is the number of males in i^{th} age-group, and P_w is the total number of males, in the world standard population.

All of the crude, age-specific, and the age-standardized rates were three-year average rates derived for each of the periods 82-84, 85-87 and 88-90.

2.5.3 Statistical testing

Statistical significance of the trend in completeness of PCa registration over three periods of time (1982-84, 85-87 and 88-90) was tested using the chi-squared test for

linear trend in proportions with 1 degree of freedom. The number of cases were recorded in a 2x3 table, in which the time variable (explanatory variable) was ordered from 1 to 3, and completeness (dependent variable) was classified into registered and missed cases of PCa, as in the following diagram:

	number of PCa cases		
year of diagnosis exposure $(x)_{+j}$	registered $(n1)_{+j}$	missed $(m1)_{+j}$	total NE_{+j}
82-84 $(x)_{+1}$	$(n1)_{+1}$	$(m1)_{+1}$	NE_{+1}
85-87 $(x)_{+2}$	$(n1)_{+2}$	$(m1)_{+2}$	NE_{+2}
88-90 $(x)_{+3}$	$(n1)_{+3}$	$(m1)_{+3}$	NE_{+3}
total	n1	m1	NE

The Chi-square value was obtained from the EPIINFO statistical calculator, using the formula

$\chi^2_{trend} = [T_1 - (n1 * T_2 / NE)]^2 / V$, with 1 degree of freedom (Schlesselman, 1982).

Where,

$T_1 = \Sigma_j (n1)_{+j} * (x)_{+j}$, $T_2 = \Sigma_j NE_{+j} * (x)_{+j}$, $T_3 = \Sigma_j NE_{+j} * (x)_{+j}^2$

and $V = \{(n1) * (m1) * (NE * T_3 - T_2^2)\} / \{NE^2 (NE - 1)\}$.

Under the null hypothesis of no trend this has a chi-square distribution on 1 degree of freedom.

Differences in completeness between age-groups and between the five regions of cancer registries were tested for statistical significance using the chi-squared test for heterogeneity. Here is an illustration of testing the association of completeness to the region of registration:

number of cases	region of registration					
	North	North-East	East	South-East	West	total
registered	$n1_1$	$n1_2$			$n1_5$	n1
missing	$m1_1$	$m1_2$			$m1_5$	m1
total estimated	NE_1	NE_2			NE_5	NE

This table gives the number of observed values (O_{rk}) in the cell of r^{th} row (r=1,2) and k^{th} column (k=1,..5). The expected value (E_{rk}) of any cell is equal to the summation of its column total (NE_k) and its row total (n1 or m1) divided by the overall total (NE).

Using the EpiInfo statistical calculator the chi-square value was obtained according to the formula, $\chi^2 = \Sigma [(O_{rk} - E_{rk})^2 / E_{rk}]$, which has, under the null hypothesis, a chi-square distribution with a degree of freedom equal to (5-1) x (2-1), as described in Dean (1994).

Note that these statistical tests are performed as if the NE's were known rather than subject to random variability. However, the test statistics correspond to alternatives calculated for relative completeness where the denominators are known quantities.

3. RESULTS

The relative completeness of SCR for PCa during the 1982-1990 period was 89.2%. It increased during this period from 87.5% in 1982 to 90.6% in 1990. However, this upward trend showed some fluctuations and the highest percentage ever reached was about 91% in 1987 (Table 7.1).

The total observed number of cases over the whole period of 1982-1990 was 11169 and that estimated by the capture-recapture method was 11388; about 2% total deficiency in ascertainment. Analysis of completeness of each of SMR1 scheme and SCR for PCa cases estimated by this method during the study period shows that SCR registered more cases than did the SMR1 scheme.

Out of 11388 cases estimated during 1982-1990, 89.2% (10139) were registered at SCR compared to 82.4% (9389) who had an SMR1 record (Table 7.2).

Table 7.3 and Figure 7.2 show the time trend in estimated completeness of SCR. Percentages of completeness have varied with time following a slightly fluctuating but eventually rising course. Between 1982 and 1987 completeness increased by almost 5%, from just over 86% to 91%. It then declined to 90.5% in 1988 and 88.1% in 1989 subsequently to rise again to 90.4% in 1990. Between 1982 and 1990 there is an increase of at least 4% in completeness.

Table 7.4 shows estimated completeness in different age-groups. Generally it varied significantly with age (χ^2=57.09, df=8, P<0.001). Out of 61 cases estimated in the age-group 35-49, only 43 (70.4%) were registered at SCR, representing the lowest estimate, compared to 91.6% (1615/1762) in the age-group 65-69 which is the highest estimate for age-specific completeness. Completeness was relatively higher in the age of 55 to 79 compared to other ages, ranging between 88.2% to 91.6%, and it

was also considerably higher in upper extreme than the lower extreme of ages (85.7% versus 70.4%).

The distribution of estimated completeness in the five regional cancer registries is shown in table 7.5. In the Northern region cancer registry only 82% of the estimated number of cases have been registered (435/531). The North-Eastern registry have covered around 92% of the estimated cases (1213/1321), the highest percentage for any region, followed next by the Western region registry which covered nearly 91% of the estimated cases.

Completeness in the Eastern and the South-Eastern registries were found to be 87.1% and 87.5%. Such differences between regional registries in completeness were found to be statistically significant (χ^2=67.84, df=4, P<0.001).

Using the three-year average shows that the estimated completeness increased by only 3% between 1982-1984 and 1988-1990 (Table 7.6). This slight change was statistically significant (χ^2=29.74, df=2, P<0.001).

Comparing the increase in the observed and the estimated incidence rates, the estimated is around 4% less than the observed rate (18.6% versus 14.6% for the crude rate and 11.5% versus 7.3% for the age-adjusted rate), and the age-adjusted rate is always less than the crude rate by nearly 7%.

Table 7.7 shows results of a robust analysis carried out after reverting the source of inconsistent matched cases from SCR to SMR1. There has been no change at all, from the original analysis, in the trend of the increase in the estimated rates. The increase in observed numbers and rates, however, were slightly reduced, as a result of this modification, and so was the increase in completeness which decreased from 3% in the original analysis to 2%.

Table 7.1: Time trend in relative completeness of SCR for prostate cancer cases recorded on SMR1 in 1982-1990

Year of admission on SMR-1	Number of cases on SMR1	Cases with matched SCR record			
		consistent matches		unmatched	
		number	%	Number	%
1982	1008	882	87.5	126	12.5
1983	939	816	86.9	123	13.1
1984	1032	897	86.9	135	13.1
1985	1014	912	89.9	102	10.1
1986	1034	937	90.6	97	9.4
1987	1070	973	90.9	97	9.1
1988	1049	949	90.5	100	9.5
1989	1174	1036	88.3	138	11.8
1990	1187	1075	90.6	112	9.4
Total cases	9,507	8,477	89.2	1,030	10.8

Table 7.2: Completeness of SCR and SMR1 for PCa cases estimated by capture-recapture method, Scotland 1982-1990

SCR	SMR1 scheme		total estimated No of cases
	present	absent	
present	8359	1780	10139 (89.2)*
absent	1030	**219**	**1249**
total	9389 (82.4)*	**1999**	**11388 (100.0)***

* Figures in parentheses are the percentages calculated from the overall estimated number of PCa cases

Figure 7.2 Estimated completeness of prostate cancer registration in Scotland 1982-1990

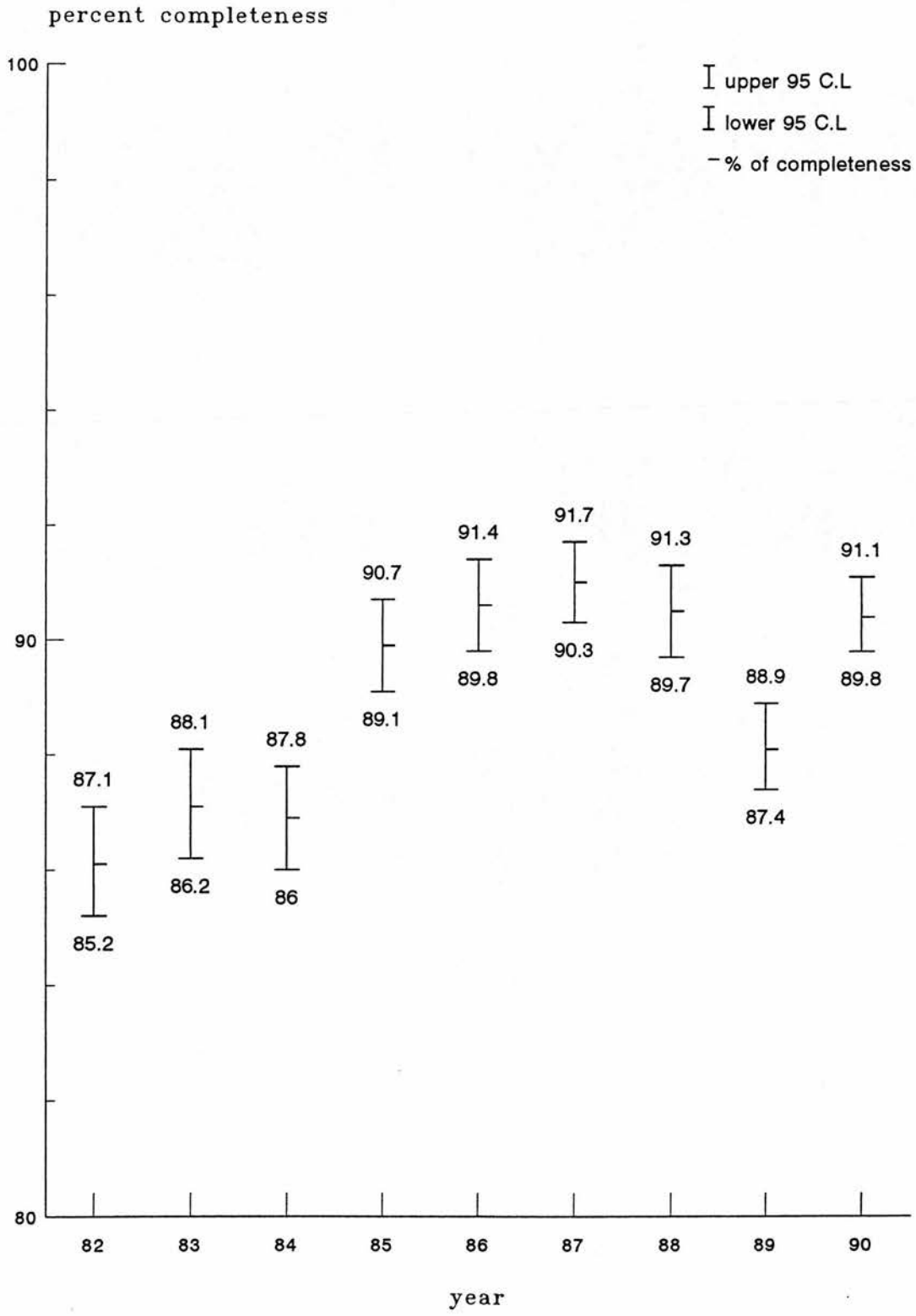


Table 7.3: Time trend in completeness of prostate cancer registration at the SCR estimated by capture-recapture method

Year of diagnosis	Observed N of cases	Estimated N of cases	Completeness %	95-C.L of completeness	
				lower	upper
1982	954	1107.87	86.1	85.2	87.1
1983	1051	1206.15	87.1	86.2	88.1
1984	1082	1245.72	86.9	86.0	87.8
1985	1108	1232.31	89.9	89.1	90.7
1986	1147	1266.10	90.6	89.8	91.4
1987	1170	1286.14	91.0	90.3	91.7
1988	1183	1306.98	90.5	89.7	91.3
1989	1213	1376.61	88.1	87.4	88.9
1990	1231	1361.54	90.4	89.8	91.1
overall	10,139	11388.31	89.0	88.8	89.3

Table 7.4 Completeness of prostate cancer registration at the SCR estimated by capture-recapture method according to patient's age

Age	Observed N of cases	Estimated N of cases	Completeness %	95-C.L. of completeness	
				lower	upper
35 - 49	43	61.05	70.4	66.5	74.8
50 - 54	116	137.16	84.6	81.6	87.7
55 - 59	354	401.18	88.2	86.9	89.6
60 - 64	876	983.51	89.1	88.2	90.0
65 - 69	1615	1762.34	91.6	91.1	92.2
70 - 74	2300	2553.03	90.1	89.6	90.6
75 - 79	2340	2618.83	89.4	88.8	89.9
80 - 84	1631	1868.18	87.3	86.6	88.1
85 +	864	1008.39	85.7	84.4	87.0

$\chi^2_{\text{heterogeneity}}$=57.09 df=8, P<0.001

Table 7.5: Completeness of prostate cancer registration at the SCR estimated by capture-recapture method according to region of registration*

Region of registration	Observed N of cases	Estimated N of cases	Completeness %	95-C.L. of completeness	
				lower	upper
North	435	530.82	82.0	80.5	83.5
North-east	1213	1321.13	91.8	91.1	92.5
East	863	990.70	87.1	85.9	88.4
South-east	2607	2978.28	87.5	86.9	88.2
West	5021	5526.66	90.9	90.6	91.2

$\chi^2_{heterogeneity}$=67.84, df=4, P<0.001

* 42 cases were missing due to unknown code.

Table 7.6: Three-year average of observed (O) and estimated* (E) incidence (crude and age-standardized) of prostate cancer among 35+ years old males** in Scotland 1982-1990

Year of diagnosis	Number of cases		Crude incidence /10^5		Age-adjusted incidence*** /10^5		Complete-ness %
	O	E	O	E	O	E	
82-84	3087	3559.99	41.4	47.8	26.1	30.3	86.7
85-87	3425	3784.48	46.1	51.0	28.1	31.1	90.5
88-90	3627	4045.52	49.1	54.8	29.1	32.5	89.7
82-84/88-90 % increase	17.5	13.64	18.6	14.6	11.5	7.3	

χ^2_{trend} =15.81 ,df=1, P<0.001 (trend of completeness).

$\chi^2_{heterogeneity}$= 29.74, df=2, P<0.001.

* Estimated incidence was obtained by capture-recapture method.

** numerators only include cases of 35 years of age and above but it is assumed that no cases had occurred below this age.

*** age was adjusted to world population by direct standardization.

Table 7.7: Three-year average of observed (O) and estimated* (E) incidence (crude and age-standardized) of prostate cancer among males after reversing the location of inconsistent matches in the original analysis, Scotland 1982-1990

Year of diagnosis	Number of cases		Crude incidence /10^5		Age-adjusted incidence** /10^5		Complete-ness %
	O	E	O	E	O	E	
82-84	3068	3561.34	41.2	47.8	26.0	30.3	86.2
85-87	3384	3788.38	45.6	51.0	27.8	31.1	89.3
88-90	3576	4048.77	48.4	54.8	28.7	32.5	88.3
82-84/88-90 % increase	16.6	13.69	17.5	14.6	10.4	7.3	

* Estimated incidence was obtained by capture-recapture method with relocation of inconsistent matches to SMR1.

4. DISCUSSION

4.1 Data reliability and completeness

An early study by Lockwood (1971) revealed very high accuracy (close to 100%) of SMR1 for personal identification data which form the basis for matching. It was also reasonably accurate for diagnoses. Similar results have been found for personal items on SCR (Brewster et al 1994).

Errors of matching between these two systems though, may have some effect on the accuracy of estimated completeness of SCR for PCa registration, and of our estimate of total number of PCa cases obtained by the capture-recapture method, by affecting the distribution of the true matches and the true non-matches in cases from the two ascertainment sources. This effect is estimated to be between 1% (Kendrick and Clarke 1993) and 2% (O'Brien F: personal communication) but, it is self-adjusting (the false positives against the false negatives).

Changes in accuracy of either source with time could affect the results. This was apparent when inaccuracies in the SMR1 records as indicators of diagnoses had not been excluded and the preliminary analysis showed markedly lower estimates of completeness in the early years of the study 74-81%, compared to the rest of the years (see 2 appendix A). This was successfully treated by identifying SCR records initiated before the study period (before 1981) and which had matched SMR1s initiated in the first years of the study period. That led to improvement in the estimates of completeness in 1982 to 1984 in the final data set starting with 86.1% in 1982 (Table 7.1), as opposed to 74% in the previous estimation, and as a result the trend in completeness became less steep.

Missing data fields have not affected estimates over time or with age, but estimates for regional cancer registries have encountered 42 cases with missing region. Discrepancy has been noticed in some of the cases with matched pairs of SMR1 and SCR (8359), in year of treatment (350), age (86) and health board code (140). These differences were treated sensibly, by adjusting the small differences using the time interval between the two dates, which was completely successful in the case of the year, or otherwise choosing one value at random (see methods section). Any possible misclassification error after that, in estimated completeness by these variables, should be small.

The SMR1 system is an event-based system where there is a record issued for every admission including those due to the same problem, and for the purpose of using it in this study as an alternative source of PCa cases to assess completeness of SCR over time it was optimal to pick up only one SMR1 record that is relevant to the diagnosis event of the disease. This was attempted at ISD but nevertheless, relating the SCR and its matched SMR1 record according to the time of diagnosis revealed some discrepancy that reached up to more than five years (Figure 1). There were 111 cases with an SMR1 record that was initiated more than one year from its matched SCR record and which is unlikely to be the one that is relevant to the diagnosis event. These SMR1s were, therefore, ignored.

Assuming that this classification of these SMR1 records is incorrect and the opposite is correct(i.e. that these SMR1 records were relevant but the SCR not) the effect would be as shown by the second analysis after the location of these SMR1s was reversed. The results of the original and this alternative analysis are shown in tables 7.6 and 7.7. Their similarity indicates that the choice of methodological

approaches is not critical. Completeness has slightly decreased from 86.7% in the original analysis to 86.2% in the alternative in 1982-84, from 90.5% to 89.3% in 1985-87 and from 89.7% to 88.3% in 1988-90. Overall, there is a reduction of 1.1% in the trend of completeness, from 3.5% to 2.4%, which could represent the amount of over-estimation of completeness of SCR due to this approach. However, treatment of the inconsistent matches in the original analysis seems to be fair given that duplicates are more likely to be a feature of an event-based recording scheme like SMR1 than it is of a patient-based cancer registry.

The 368 cases on the Registrar General death records who died with prostate cancer between 1982 and 1990 and have neither SMR1 nor SCR record were excluded, as because of their unknown date of diagnosis and a possible detection bias (for autopsy-diagnosed cases) their inclusion would distort the trend in estimated completeness.

4.2 Completeness and independence of the two sources

The ratio of registered to estimated number of PCa cases would be an unbiased estimate of completeness of registration at SCR if the ascertainment of cases by SCR and SMR1 schemes were independent of each other, but, any deviation from this will affect reliability of these estimates (under or over estimation), depending on whether the deviation was toward mutual exclusiveness or to the opposite direction of complete dependence (as in the following table).

Dependence of sources	NEGATIVE DEPENDENCE	*INDEPENDENCE*	POSITIVE DEPENDENCE
Total number of PCa cases	OVER-ESTIMATION	*UNBIASED ESTIMATE*	UNDER-ESTIMATION
Completeness	UNDER-ESTIMATION	*UNBIASED ESTIMATE*	OVER-ESTIMATION

Determination of the amount and direction of this bias is important for interpretation of estimated completeness and their change with time, age and place, but is not feasible analytically with the two-source capture-recapture method (Wittes et al, 1974). However, the issue can be argued logically to reach a sensible understanding of the amount of change in the incidence of PCa that can be ascribed to progress in completeness of case registration. Two points are important here; the state of independence at the beginning of the study and its change over the study period. As far as the first point is concerned, given the organizational liaison between SCR and SMR1 schemes within ISD and the possibility that the same hospital staff were responsible for notifying both schemes, it is unlikely that they were absolutely independent, and a certain amount of positive dependence between them would rather be a very likely possibility. Accordingly, the 86.1% completeness estimated in 1982 should be an over-estimate of the true completeness in that year. Yet, this effect has been counteracted slightly by depriving SMR1 of the 111 inconsistent matches, while acknowledging them for SCR, which obviously may have led to over-estimation of

number of cases diagnosed and thus under-estimation of completeness. The outcome of this argument is that the 1982 estimate and its confidence limits are reasonable representatives of the true completeness and its two extremes. Even when some positive dependence remained without adjustment, the estimate of the number of cases and its confidence limits will be useful measures of lower extremes, and completeness percentage and its limits as the upper extremes of the true values (Hook and Regal, 1992). As far as temporal change in independence of sources is concerned, despite the undoubted periodic reviews of the two programmes and efforts to improve the collaboration between the two there is no reason to believe that these had a significant progressive effect on the sources' independence over the study period. The record linkage project which is the most important feature of this collaboration began in mid-1989 (Kendrick and Clarke, 1993), and presumably would have taken sometime before it was ready for implementation. It is therefore safe to say that most of the change in estimated completeness with time is likely to be real and can be attributed to improvement in coverage, with only a slight change due to the increased dependence between the two schemes. Given this limitation of the capture-recapture methods as tools for estimating completeness, it is still superior to traditionally used incidence to mortality ratio (Robles et al 1988) but not as accurate as an independent case ascertainment survey (Schouten et al 1994).

4.3 Completeness of SCR for PCa registration

Bearing in mind the small effect of matching error, completeness of PCa registrations in Scotland in 1982 (86.1%) is higher than in the North-Western region of England in 1974-75 which was estimated at 80.7% (Benn et al 1982), but is lower

than the 93.5% completeness in Ontario (Canada) for the same year (Robles et al 1988) and lower than the 1978 estimate (98%) for Sweden (Mattsson et al 1985). In the Swedish study however, 35% of the cases were considered non-registrable (excluded) due to scarce or incomplete information which could be a potential selection bias leading to over-estimation, if the excluded cases were not actually on the cancer register.

The 1990 estimate of completeness of PCa registration in Scotland (90.4%) is much higher than that (70%) reported by Seddon and Williams (1997) for the same year registrations for Merseyside and Cheshire Cancer Registry (UK), but is still lower than estimates from Canada (Robles et al 1988) and Sweden (Mattsson et al 1985). However, these differences between Scotland and other places cannot be interpreted without knowing exactly the differences in registration, diagnostic practices and the error due to deviation from the rule of independence.

4.4 Trend in completeness of SCR for PCa registration

Improvement in cancer registration with time is always anticipated (Esteve et al 1994) and the first few years are the worst affected by under-reporting (Nwene and Smith 1982). At the time of this study period more than two decades would have elapsed since the Scottish Cancer Registry had begun operating as a national population-based system (Black et al 1993); this period is long enough to witness a substantial amount of progress in reporting efficiency. During the study period completeness of PCa registration has improved by 4% from 86.1% in 1982 to 90.4% in 1990 (Table 7.3). After removing most random fluctuation, by taking the three-year average percentage of completeness, 3% improvement was recorded (Table 7.6).

Such a small amount of progress is not surprising and greater achievements must have taken place sometime before that. Nevertheless, the small improvement is statistically highly significant (χ^2_{trend} =15.8, df=1, P<0.001), and a healthy characteristic in the system indicating the continuous momentum to achieve the target of 100% completeness.

A potential error leading to over-estimation in the 3% increase could come from the treatment of cases with inconsistent matches in the way explained earlier. An opposite approach has been shown to reduce this percentage to 2% (Table 7.7). But as explained earlier the 3% is the most likely accurate level, especially that the 2% is based on ignoring existing SCR records of some cases. In the annual completeness trend two successive points of decline in 1988 and in 1989 were noticed (Table 7.3), which are hard to explain other than as chance events.

The SCR estimated completeness was, nevertheless, lower than one might hope, and after allowing for the minor effects of matching errors and data manipulation, researchers should be made aware of it. There is no doubt that the record linkage facility can contribute a great deal to overcome this problem. Other methods of monitoring particularly independent surveys should be considered.

4.5 Completeness variation with age and by region of cancer registry

The SCR estimated completeness for PCa registration has also shown significant variation with patient's age at diagnosis (χ^2=57.1, df=8, P<0.001). The low completeness in 35 to 49 year-old men could be due to chance effects for the small number of cases (43) but, the particularly lower coverage of men in the upper extreme of age compared to those in younger ages is consistent with findings from other studies. Assessing completeness of registration against death records in the

West of Scotland Haddow (1968) has found it to be less than 50% in 80 to 89 year-old individuals and even lower in the higher age. Schouten et al (1994) from the Netherlands reported lower completeness for people 75 year-old or more than for younger ages and in Sweden, Mattsson et al (1985) found that completeness of cancer registration was the lowest in the very young (less than 15 years) and higher in young men in the age 15-69 than the older men. Taking into account the differences in age classification and cancer sites covered in these studies, non-notification in general can be due to reasons which might prevail more among elderly.

Mattsson et al (1985) have related variation of completeness by age and histological verification to: the lack of microscopic confirmation leaving the decision of notification wholly to the clinician, number of health service departments involved in diagnosis (the more the better is the notification) and the lack of in-patient care, which is rare for common cancers. One possible reason for prostate cancer in particular is that the treatment for men in the oldest age-group is often not more than just 'watch and wait'; ambiguity of the term "date treatment commenced" on cancer notification forms could be understood by some of the staff as an indication of reporting the treated patients only, so that these cases may not be reported.

Completeness also varied significantly among the five regional cancer registries (χ^2=67.8, df=4, P<0.001). With no obvious reason to believe in variation between regional cancer registries in the independence of SMR1 and SCR, variation between regional registries could be due to differences in case ascertainment sources and procedures. Staff competence and familiarity with registration procedures could also account for some of these differences (Zippin and Lum 1993). Transferral of a patient between health boards for further investigation or treatment may assign him to two

different regions. Some cases in this study did have a different health board code on SMR1 from the one on the SCR. This was solved by choosing a single region using a formal algorithm. This besides the 42 cases with no region specified, could have had a slight effect on the regional distribution of completeness.

4.6 Implications for interpretation of time trends in PCa incidence

Between the periods 1982-1984 and 1988-1990, the total increase in the absolute number of observed (registered) cases of PCa in Scotland was nearly 17.5% (Table 7.6). The crude rates calculated for both observed and estimated cases have a gain of 1% over the increase in the corresponding absolute numbers owing to the slight decline in the estimated total male population in Scotland (ISD 1991). Following age-adjustment, by standardizing age-specific rates to the world population, the increase in rates has gone down by about 7% to 11.5% for the observed and 7.3% for the estimated age-adjusted rates; this amount represents the effect of change in age structure of the Scottish population.

The difference between observed and estimated values is around 4% which is attributable to improvement in completeness, while the remaining 7.3% increase in the estimated age-adjusted rate represents the unexplained part of the trend.

It is therefore reasonable to conclude that out of the 18.6% increase in the observed crude rate, around 7% (37.8% of all change) is due to ageing of population, 4% (21.6% of the total change) due improvement in completeness and 7.3% (39.5% of the total change) is yet to be explained. Combining the ageing and completeness components will explain the largest part of the change. The remaining 7.3% will obviously include an anticipated component from improved case detection methods,

particularly the increased detection of incidental carcinomas as a result of more use of TURP in the treatment of BPH. It will also include the possible genuine component.

CHAPTER VIII

CLASSIFICATION OF INCIDENTAL PROSTATE CANCER CASES FROM CASE NOTES REVIEW

1. INTRODUCTION

Boyle et al (1993) defined incidental prostate cancer as "... tumours found unexpectedly by the pathologist following prostatectomy for BPH ...". If the prostatectomy is TURP, these cases can be called "TURP-detected incidental" or, as a short hand, "TURINC" carcinoma. In the TNM classification TURINC PCa cases are $T1_a$ and $T1_b$ tumours that are not palpable and not visible by imaging (Schroeder et al 1992). In this study the same definition will be used except that ultrasound results are not available and some precautions will be taken to minimise likely false positive and false negative palpation (DRE) results (see methods section).

Identification of these "TURP-detected incidental" or "TURINC" PCa, in Scotland is important for studying their trend and estimating the artefactual increase they generate in the overall trend of PCa. This requires some information about the clinical examinations and investigations that have been done for each prostate cancer patient before diagnosis was made, which will allow us to separate TURP operations that have actually led to the incidental detection of cancer from those that have been conducted to confirm or treat clinically-diagnosed cases, and hopefully to understand the extent of the disease. This clinical information is not normally available from routine data sources and must be extracted from patients' hospital case notes. This task, however, is difficult and expensive to do nationwide on a retrospective basis.

The present chapter focuses on a case-note review of a sample of cases diagnosed in Lothian. The aim is firstly to classify PCa cases there as "TURINC" or not, and, secondly,

to relate this to factors which are routinely available so that these can, in probabilistic terms, quantify TURINC cases. The ultimate objective is to apply this latter classification to the routine national data on prostate cancer incidence in order to have an estimate of the artefact in the disease trend caused by TURP. The present chapter is restricted to the fieldwork and the problems encountered in establishing this classification from hospital case note review.

To classify cases in the fieldwork study, shortcomings and difficulties related to availability, completeness and accuracy of data, and readability of clinical examination results can be encountered.

DRE is a major determinant of a case being TURINC or not. Therefore, its accuracy is important to the classifcation. DRE has been described, as highly subjective, and its findings are difficult to record accurately (Varenhorst et al 1993). Peeling et al (1986) related the accuracy of interpretation of DRE to the experience and care of the examiner. Malignancy is suspected by DRE if there is induration or firmness of the gland, asymmetry or nodularity or fixation. However, other non-malignant prostatic conditions, including BPH, may exhibit the signs of malignancy and diagnosed as cancer (Babayan 1989, McNeal et al 1988a). In contrast, a malignant tumour may be soft so that it may be misdiagnosed as a benign lesion (Byar et al 1972).

Definition of TURP-detected incidental carcinoma (see 2.3.6 below) requires accurate staging and those false positive and false negative errors of DRE would result into staging errors for T1/T2 cancers. A consensus group of scientists met to discuss the 1992 modifications of the TNM staging system recommend a repeat DRE to improve its reliability (Schroeder et al 1992).

An error in staging can occur because of residual parts of tumours found on second TURP or prostatectomy operations. This was mainly noticed as understaging $T1_b$ to $T1_a$ (Voges et al 1992; Carroll et al 1985; Bridges et al 1983; McMillen and Wettlaufer 1976) but, unusually, some clinically staged T1 tumours may be pT3+ stage on pathology (Larsen et al 1991; Catalona and Stein 1982). However, while understaging $T1_b$ to $T1_a$ does not affect the classification of a case as incidental or not incidental, for T3+ to T1 understaging to be considered as an error of incidental classification, DRE must have missed the T3+ malignant tumour, a presumption which is unlikely; DRE is sensitive enough to detect such high stage tumour (Schmidt 1992).

Under these circumstances, this study will classify cases, into TURP-detected incidental and other cases, following precisely specified standard criteria to interpret the clinical findings of DRE, TRUS and bone scan.

2. SUBJECTS AND METHODS

2.1 Study sample

A data file of prostate cancer cases registered at SCR, for Lothian, during the period 1981-1990 was obtained, from ISD of the Scottish National Health Service. It contains patient's identification number, cancer registration details of PCa site code and date of registration, and data on the first record on the SMR1 scheme for each of PCa diagnosis, TURP operation and BPH diagnosis. These records will be referred to as the SMR1 for PCa etc.

From this file, a study population was selected to be those patients with primary prostate cancer who were registered in Lothian in the years 82-84 or 88-90, aged 55-79 years at the time. Eight hundred and thirty-eight cases were identified as the study

population. Among them, a case was a potential candidate for selection for the review if the SCR and SMR1 information did not exclude the possibility of the case being incidental (i.e there was no SMR1 for BPH). These cases were classified into groups according to SMR criteria in the following order:

1a. The time from the TURP date to the admission date on the SMR1 for PCa (or registration date if there is no SMR1 for PCa) is greater than 0 but ≤ 6 months.

1b. BPH and PCa are recorded together on any one of the SMR1s for PCa, BPH or TURP, i.e.

BPH is recorded on the SMR1 for PCa;

or PCa is recorded on the SMR1 for BPH;

or both are recorded on the SMR1 for TURP.

[Note that this often means that two or even three of the SMR1s are identical].

1c. BPH is recorded on the SMR1 for TURP but PCa is not.

2. There is an SMR1 for BPH but neither PCa nor TURP are recorded there.

Out of a total of 838 cases, 202 were selected according to these criteria. Of these, there were 66, 17 and 64 cases in the groups 1a-c, respectively, all of which were selected for review. Fifty-five cases were in the group 2 of which 25 were selected for review at random (by assigning a random digit between 0 and 1 to every case and choosing the ones with a digit of more than 0.5).

Since the objective was to judge whether the selected cases were incidental from their clinical history and examinations and relate this to routine data, it was important to ensure blindness of the investigator to the SMR information that might influence his judgement. This was achieved by creating a working copy of the sample data file, without these items,

from which a list showing patients' name, date of birth, case note number, and hospital of treatment was prepared for case note retrieval.

2.2 Data accessibility and collection

Before accessing each patient's case notes, permission was obtained from the treating consultant and passed to the medical records department to allow access to the case notes. Hospitals were then visited by the investigator to review the case notes and to abstract the required information. Missing or incomplete records from every hospital in the study have been chased in other hospitals in Lothian region to secure maximum coverage of study records.

Data required for the study were urological examinations, investigations and prostatic operations undertaken before and until two months after diagnosis of prostate cancer. These include findings of DRE, trans-rectal ultrasound, bone scan, prostate aspiration or needle biopsy, TURP and other prostatic operations, autopsy, T staging, local extension and other metastases. Frequently, more than one DRE had been conducted. Information was transcribed as it appears in the case notes to a pre-designed data collection form (appendix B).

2.3 Data coding and interpretation

Coding was assigned for individual DRE suspicion of malignancy, appropriateness of DRE suspicion, overall DRE suspicion, evidence of local extension and distant metastases, and, finally, incidental status of the case, according to pre-set conditions and criteria. Details of these are shown in appendix D. Coded data were transferred to a special coding form (appendix C) before they were entered and saved in an EPIINFO data file for analysis.

2.3.1 Method and date of diagnosis

The method of diagnosis is defined to be the most valid and earliest procedure by which firm cancer diagnosis was established. Validity was the criterion applied first and in this respect, histological verification of cancer from prostatic specimen obtained by means of prostatectomy or biopsy is the most valid method. Histology of biopsy specimens from a secondary site (e.g. lymph node) suggesting prostate as the primary is next followed by autopsy. If more than one procedure of similar validity was performed at the same date, the method of diagnosis will be a combination of these procedures. If there was no microscopic confirmation, bone scan, other clinical investigation or DRE (if it was the only procedure suspected malignancy) would be the method of diagnosis. The date of diagnosis was the date of the procedure taken as the method of diagnosis (or death if earlier).

2.3.2 DRE suspicion, overall DRE suspicion and its appropriateness

(a) To ensure consistency in DRE findings, only DRE performed by urologists were included in the study.

(b) Relevance of each individual pre-diagnostic DRE to the ultimate diagnosis of PCa and, at the same time, allowance for possible delay between the clinical examination and subsequent management of the case have been taken care of by including, in general, only those DREs that were performed in the 2 month period preceding diagnosis. However, if no DRE was conducted in that interval, then the most recent DRE done up to 12 months before diagnosis was taken. These are referred to as 'valid' DREs.

(c) Coding of DRE suspicion of malignancy was done on a five-point scale ranging from 1 for definitely suspicious to 5 for definitely not suspicious, according to DRE signs and diagnosis labels given by the urologist (appendix D).

(d) When more than one DRE was available a code of suspicion was first assigned for each DRE. Then from these an overall DRE suspicion summary code was derived. The overall DRE takes the same code as the valid DREs if these are all the same. Otherwise, if none of them was done under general anaesthesia, the overall DRE takes the least definite code if all are on the same side (i.e. 1-2 or 4-5); when disagreement is wide (i.e. they are not on the same side of suspicion), the overall DRE is 'equivocal'. If one DRE was done under general anaesthesia, the overall DRE will normally take its code. If however the code of the DRE that was done under anaesthesia was 'definitely suspicious' and another DRE code was at the opposite extreme ('definitely not suspicious'), the overall DRE code will be 'probably suspicious'; similar modifications apply if the general anaesthesia DRE code is 'definitely not suspicious' but the other is 'definitely suspicious' (see appendix D). The DRE done under general anaesthesia was favoured because it has been found to be more reliable in assessing the tumour extent (Babayan 1989).

(e) If malignancy was suspected on overall DRE or the overall DRE was equivocal the overall DRE suspicion was assessed, histologically, for its appropriateness i.e. whether it could be relevant to the diagnosed tumour or a false positive. If the tumour was pathologically small extent tumour (see 2.3.4 below), or a lesion biopsy following the DRE was negative then findings were considered inappropriate (i.e. false positives - appendix D).

2.3.3 Clinic versus general anaesthesia DRE agreement

Variation in suspicion codes, in cases with more than one valid DRE, was examined by comparing the code (or the 'average' code when there is more than one) of DREs done at the clinic with the ones done under general anaesthesia. The average code for clinic DRE's was obtained in the same way as previously described for overall DRE. Exact agreement was calculated as a percentage of the total cases involved in the comparison with the two codes identical. Minor and major disagreement were also calculated. Minor disagreement refers to variation in the two codes within 1-3 or 3-5, and beyond that the disagreement is considered major.

2.3.4 Tumour extent

Tumour extent was assessed for cases diagnosed by TURP according to the pathologist's estimation of the extent of tissue specimen affected by tumour. A case is said to be of small extent if, after examination of the whole specimen received, the tumour has occupied 5% or less of the specimen or 3 foci or less. This extent is similar to T1a class tumours in the fourth edition and its revision of the TNM classifications of tumours (Hermaneck and Sobin 1987, 1992). To enable extent assessment in cases where the pathologist mentions only the number of chips involved by the tumour, it was decided to consider a tumour extent small if 3 chips or less were involved following Sheldon et al (1980) in their classification of focal incidental carcinoma. Apart from cases with small extent tumours, all other cases were classified in one group as large or unknown tumour extent.

2.3.5 Post-TURP investigations

To ensure that all the investigations related to the diagnosis of cancer are incorporated in the classification of cases, findings of DRE, bone scan and other

investigations were considered related to the diagnosis (and hence relevant as evidence of local or distant metastases) if they were done before or up to 2 months after the diagnosis date. The choice on the two-month period is based on the time distribution of cases which have been examined by bone scan or given a T stage as can be seen in figures 8.1 and 8.2. The purpose of this is to allow for possible delays in conducting some investigations, like bone scan and T-staging. On the other hand, the time period should not be long enough to allow tumour progression post-diagnosis.

2.3.6 Classification of cases (TURP-detected incidental and all other cases)

Classification of cases into "TURINC" or "NOT TURINC" was done on the bases of DRE suspicion of cancer and its appropriateness, evidence of local extension (by describing the tumour as locally advanced or T3 stage) and evidence of distant metastases on bone scan or other investigational procedures (e.g. ultrasound or computerised tomography).

In terms of these criteria, a case is classified as "TURINC" if:

a. it was diagnosed by TURP; and

b. there was no suspicion of malignancy by pre-TURP DRE (or DRE suspicion was found by biopsy to be not appropriate), or other investigations such as bone scan, TRUS and x-ray; and

c. neither local extension nor distant metastases have been mentioned up to two months after diagnosis.

The case was classified as "NOT TURINC" if, TURP was not done or cancer was suspected by pre-TURP DRE (unless DRE suspicion was found by biopsy to be not

appropriate) or other investigative procedures mentioned earlier; or local extension or distant metastasis were mentioned up to two months after TURP (see appendix D).

The TURINC cases as defined by this study are basically $T1_a$ and $T1_b$ tumours in the T-categories of the TNM classification of prostate cancer in that they are not palpable (Shroeder et al 1992). The difference is that in the TNM classification, these carcinomas should not be visible by ultrasonography (TRUS) but information on the procedure was not available for this study. In addition, the two-month period that was permitted for post-diagnosis clinical findings, applies more restriction to the definition of the incidental cases in this study.

The two classes "TURINC" and "NOT TURINC" were further subdivided each into two subclasses "definite" and "probable". The distinctions between a "definitely TURINC" and a "probably TURINC" case are, firstly, that in the first the overall DRE must have been definitely not suspicious of cancer and, secondly, a bone scan should have been conducted and ruled out cancer.

A case is "definitely NOT TURINC" if TURP was not done or, if TURP findings were negative for cancer or positive but associated with a definitely suspicious DRE, positive metastases, or positive biopsy finding.

The "probably NOT TURINC" cases are those in which DRE was probably suspicious and not inappropriate, or DRE was not suspicious before but after diagnosis (up to two months), or T2 stage was mentioned before diagnosis, or local extension of the tumour or T3 stage were mentioned before or up to two months after the diagnosis. Cases that were not possible to classify, either because DRE findings were missing or not certain, or information was not sufficient, have been assigned to the uncertain class (code 3).

2.4 Estimated number of TURINC PCa in the sample

2.4.1 Estimated total number

The total number of TURINC PCa cases in the sample was estimated by taking into account the possible true state of unclassifiable cases and those with missing notes. Any such case who had died of prostate cancer is taken as NOT TURINC. Other missing and unclassifiable cases were considered according to one of the following three assumptions:

assumption 1 that none of them is TURINC.

assumption 2 that all of them are TURINC.

assumption 3 that they have the same chance of being TURINC, as the classifiable cases, conditional on the SMR information (see below).

(a) Derivation of the estimates:

1. Minimum estimate: it is based on assumption 1 and is equal to the number of TURINC cases observed from the valid case notes.

2. Maximum estimate: it is based on assumption 2 and is equal to the sum of observed TURINC cases and all missing cases.

3. Average estimate: it is based on assumption 3 and is equal to the sum of observed TURINC cases and those estimated among missing cases (See appendix E for details of calculations).

2.4.2 Estimated number of TURINC cases by period of registration

Estimation of the number of TURINC cases in the sample in each of the two study periods 82-84 and 88-90 follows the same assumptions and methods of the total estimate.

2.5 Estimation of number of TURINC cases in the study population

2.5.1 estimated total number

The sample includes all cases in the study population that may be TURINC, except for the fourth sampling group where 25 out of 55 cases were chosen at random for review (see section 2.1). Therefore, the number of TURINC cases in the study population is formed of two components:

(a) minimum, maximum and average estimates of the number of cases in the sample (as was obtained in section 2.4.1).

(b) minimum, maximum and average estimates of the number of TURINC among the unselected batch (30 cases) of the fourth sampling group.

The second component was determined by applying the percentages of TURINC cases in the selected batch of the group, assuming equal chances of being TURINC case for the two batches. Calculations of these percentages are given in detail in appendix E.

2.5.2 estimated number of TURINC cases by period of registration

Estimated (minimum, maximum and average) numbers of TURINC cases in the study population in each of the two periods 82-84 and 88-90 is composed of; (1) their count in the sample in each period as has been estimated in section 2.4.2, (2) minimum, maximum and average number of these cases in the unselected batch of fourth sampling group in the same period. The latter were obtained by the same method in 2.5.1 but using here the period-specific percentages of TURINC cases in the selected batch (see appendix E).

2.5.3 Proportional registration ratio and population rates of TURINC and NOT TURINC cases in the study population

Total and period-specific proportional registration ratios (PRR) of TURINC and NOT TURINC cases were calculated to show trends in the relative contribution of the TURINC cases to the total registered cases in the study population.

Overall and period-specific average registration (incidence) rates of TURINC and NOT TURINC cases were truncated crude rates estimated for every 100,000 person-years of the target population, i.e. men aged 55-79 who resided in Lothian during the two periods 82-84 and 88-90.

Changes in rates over time was estimated by the percentage change in the 1982-84 rate (base-period rate) between the two periods.

3. RESULTS

3.1 Record Availability

Out of 172 cases selected for review, clinical case notes of 15 (8.7%) could not be traced and of 7 (4.1%) were judged inadequate for diagnostic information. Of the 150 cases with adequate notes, evidence of cancer was lacking in 2 and in a further case cancer was secondary to a primary lung cancer. So, 147 case notes (85.5%) of PCa were available for the analysis. Availability and data adequacy varied with period of registration at SCR. For cases registered in 88-90, 92.7% (86/96) of their records were available and adequate, compared to 80.3% (61/76) for cases registered in 82-84 (Table 8.1).

3.2 Digital Rectal Examination (DRE) Suspicion of Cancer

A digital rectal examination (DRE) had been performed by the urologist in a clinic in all, except 7, of the 147 cases but 13 of these have no DRE in the twelve-month period

preceding diagnosis. Therefore, 20 cases had no valid clinical DRE for assessing DRE suspicion. However, in 6 of these 20, and in a further 34 cases, DRE had been done under general anaesthesia. Therefore, out of all 147 cases, only 14 (9.5%) have no valid (pre-diagnostic) DRE result, whereas 84 (57.1%) have one, 38 (25.9%) have two and 11 (7.5%) cases have three valid DREs done in the clinic or under general anaesthesia. In 16 out of 84 cases with one valid DRE and in 4 out of 38 cases with two valid DREs, the clinic DRE was done 2-12 months before diagnosis.

The results of these valid DREs have been used to determine overall DRE suspicion for the 133 cases. The overall DRE suspicion code ranged from 'definitely suspicious' to 'definitely not suspicious' DRE (Figure 8.3).

The overall DRE was suspicious of cancer in 32% (47) and not suspicious in 57.1% (84) of all cases. Of suspicious cases DRE was definitely suspicious in 30 and probably suspicious in 17 cases and of un-suspicious cases it was definitely not suspicious in 64 and probably not suspicious in 20. In just 2 (1.4%) cases, overall DRE findings were equivocal; this included one case in which findings from two valid clinic DREs ten days apart were contradictory to each other (definitely suspicious in one and definitely not suspicious in the other).

Suspicion of DRE was assessed against biopsy or TURP findings for its appropriateness and the result is shown in table 8.2. This assessment was applied to 49 cases in which DRE was suspicious or equivocal. Generally, DRE suspicion for cancer was appropriate (relevant) to the diagnosed tumour in most of these cases, with 1 case only (0.7%) in which DRE was found to be inappropriate. This case had a definitely suspicious DRE but a prostatic biopsy of the lesion less than 2 months after DRE was

negative for cancer. There was no indication of inappropriateness for the two equivocal overall DREs.

Tables 8.3 - 8.5 show variation in findings of individual DREs, for the same cases. Also cross-matching of the suspicion code (or the average code if there are more than one DRE) of examinations done in the clinic with that of examination under general anaesthesia (g.a.) is shown. In 24 cases with 2 DREs (one of them was under g.a.), 16 cases (66.7%) had identical suspicion codes. Minor differences were noticed in 4 and major differences in 4 cases (16.7%) - Table 8.3. The DRE done under anaesthesia was more likely to suspect cancer than clinic DRE (10 versus 6 cases).

Variability was more among cases with 3 valid DREs (Table 8.4). Exact agreement was found in 50% (5/10), while minor and major differences were noticed in 30% and 20%, respectively. The overall exact agreement between the two examinations in cases with 2 or more valid DREs is 61.8%(21/34). Minor difference was noticed in 7 cases(20.6%) and major difference in 6 (17.6%). DRE under anaesthesia showed slightly more suspicion of cancer than the clinic DRE (17 against 13)- Table 8.5. Kappa statistics showed that agreement between general anaesthesia and clinic DREs was good (k=0.62).

3.3 Other Procedures

Bone scan examination was done in 78.9% of the cases (116/147), but only for 76 (51.7%) cases was the procedure done before the specified time limit of 2 months after diagnosis (see methods). In 21 of these 76 (27.6%), findings were suggestive of PCa, including 1 case in which this examination was the only evidence of the disease.

Other findings indicative of distant metastases (e.g. ultrasound or skeleton survey) were present in 7 cases including one case with a positive lymph node. Clinical T-staging, according to the TNM classification was mentioned in 70 (47.6%) of the cases, but only

for 41 (27.9%) cases was staging mentioned within the 2-month time limit. Local extension of the tumour was described in 9 cases, all of them were within that time limit.

3.4 Method of Diagnosis

The distribution of cases according to prostatic biopsy and TURP histological results is shown in table 8.6. One hundred and thirty eight cases (93.9% of the total) have had a TURP and cancer was histologically confirmed from 128 (87.1%). Of these 128 cases, cancer was also confirmed from prostatic biopsy done before TURP in 1 case and concurrently with TURP in another case. Cancer was histologically confirmed from biopsy in an extra 11 cases.

So, a total of 139 cases were histologically confirmed by one or both procedures and cancer diagnosis was first established from TURP in 126 cases (85.7% of all cases), from prostatic biopsy in 12 (8.2%), and from both procedures at the same time in 1 (0.7%) case. Of 8 cases remaining from the 147 cases, diagnosis was established by histological examination of tissue specimens from trans-vesical prostatectomy in 2 cases (1.4%), lymph node biopsy referring to prostatic origin in 1 and from autopsy in 4 cases (2.7%). For 1 case histology was not available and diagnosis was established from a bone scan suggesting prostate as a primary site (Figure 8.4).

3.5 Pathological extent of tumours found on TURP

Pathological extent of the malignant tumour in cancer cases confirmed or diagnosed from TURP tissue specimens, shows that in 32 out of 128 cases (21.8%) the tumour was of T1a extent, while in the rest (96 cases) tumour extent was either more than T1a or could not be determined from the available description.

3.6 Classification of Cases into TURINC and others

Out of 147 cases for which case notes were reviewed, successfully, 79 (53.7%) were classified as "TURINC", and 63 (42.9%) as "NOT TURINC". Only in 5 (3.4%) cases, was such classification not possible (Figure 8.5).

Table 8.7 shows incidental status according to pathological extent of the tumour. All, but 1, of the 32 cases in which the tumour was of small extent were "TURINC". This case was "NOT TURINC" because the bone scan was positive. Of the cases with large or unknown tumour extent 48 were "TURINC" and 43 were "NOT TURINC".

The classification in relation to overall DRE suspicion is illustrated in Table 8.8. In what appears at first to be contradictory to the criteria of classification, one of the "TURINC" cases had a definitely suspicious overall DRE, and 2 cases had no valid DRE at all. Similarly, 8 cases from the "NOT TURINC" group had an overall DRE that was not suspicious for cancer, 1 case had an uncertain DRE and another 8 had no DRE. In the "TURINC" case which was suspected by DRE, a prostatic biopsy of the lesion which followed was negative for cancer (hence suspicion was probably not appropriate). The 2 "TURINC" cases which had no DRE had a tumour of T1a extent. Cases with non-suspicious, equivocal or no DRE in the "NOT TURINC" group all had local and/or distant metastases.

According to the criteria of classification, "TURINC" cases may or may not have a bone scan done up to 2 months after diagnosis, but if it was done it must have been negative. Of 79 "TURINC" cases 32 (40.5%) were confirmed to be negative for metastasis by bone scan, while 25 (31.6%) had a bone scan done after the 2-month period and 22 (27.8%) had no bone scan at all. However, out of the 25 cases in which the

procedure was done late, 22 were negative for bone metastasis. Twenty of "NOT TURINC" cases (31.7%) and 3 of the 5 "uncertain" cases have had a bone scan that was negative for metastasis (Table 8.9).

In relation to time of registration, out of 76 cases studied in 82-84, 30 (39.5%) are "TURINC", compared to 49 out of 93 (52.7%) in 88-90. The NOT TURINC cases have slightly increased from 27 (35.5%) to 36 (38.7%) cases between the two periods (Table 8.10). The percentages of unclassifiable and with missing notes have decreased.

Each of the two main groups of "TURINC" and "NOT TURINC" cases, was divided into "definite" and "probable" subgroups. Among 79 "TURINC" cases, 24 were "definite" and 55 were "probable", and among the other group, 51 were "definite" and 12 were "probable".

In relation to overall DRE, pathological extent of the tumour and bone scan findings, all cases in the "definitely TURINC" subgroup were definitely not suspected by DRE, had bone scan done within the 2-month time limit which was negative, and 16.7% of them (4/24) have a small extent tumour. The three cases in the "TURINC" group in which a bone scan was positive for metastasis but conducted more than 2 months after diagnosis, as mentioned above, are in the "probably TURINC" subgroup.

Twenty-nine of 30 cases with definitely suspicious DRE, and all cases with positive bone scan (done within the time limit) were in the "definitely NOT TURINC" subgroup. Of "NOT TURINC" cases with bone scan done late (13), 4 were positive for bone metastasis of which 3 are in the "definitely NOT TURINC" subgroup.

3.7 Estimated proportional registration ratio (PRR) and incidence rate of TURINC and other cases in study population

It was estimated that between 10.4% and 13.3% of patients aged 55-79 years and diagnosed in Lothian during the years 1982-84 and 1988-90, were TURP-detected incidental (TURINC) cases, with an average of 11.7%. The estimated average PRR of these cases has increased from 9.6% in 82-84 to 13.7% in 88-90. The minimum and maximum estimated PRR have increased from 7.6 to 13% and from 11.8 to 14.6% respectively. Accordingly, the PRR of the other cases (NOT TURINC) has decreased from an average of 90.4% to 86.5%. On average, of the 24 total increase in the registered cases, the "TURINC" cases have contributed 20 (83.3%) compared to 4 (16.7%) for the other cases (Table 8.11).

For every 100,000 men aged 55 to 79 years who resided in Lothian during the study period there were about 196 patients per year diagnosed with prostate cancer. This truncated crude incidence rate has increased by 7.8% between 1982-84 and 1988-90; from 188.5 to 203.2/100,000 person-years. The estimated average incidence rate of "TURINC" and other cases were 22.9 and 172.9/100,000 person-years, respectively. The average incidence rate of "TURINC" cases among 55-79 year-old men, was estimated at 18.1 per 100,000 person-years during the period 1982-84. That rate has increased by 53.6%, to 27.8 in 1988-90, compared to a 2.9% increase in the estimated average incidence of other cases from 170.4 to 175.4 per 100,000 person-years (Table 8.12).

Table 8.1 Number and percentage of case note availability by year of registration in a sample of PCa patients in Lothian

Year of registration	Case notes availability				
	Available & complete	Available & adequate	Available but inadequate	Not available	Total
1982-84	44 (57.9)	17 (22.4)	4 (5.3)	11 (14.5)	76 (100)
1988-90	60* (62.5)	29 (30.2)	3 (3.1)	4 (4.2)	96 (100)
Total	104* (60.5)	46 (26.7)	7 (4.1)	15 (8.7)	172* (100)

Figures in parentheses are percentages calculated from the overall total
* 3 cases were not prostate cancer (2) or secondary PCa (1)

Table 8.2 Appropriateness of overall DRE suspicion of PCa in a Lothian sample of hospital case notes*

Overall DRE	Appropriateness of DRE suspicion of cancer					
	DNA[1]	PNA[2]	Equivocal	PA[3]	DA[4]	Total
Definitely suspicious	-	1 (2.0)	-	-	29 (59.2)	30 (61.2)
Probably suspicious	-	-	-	13 (26.5)	4 (8.2)	17 (34.7)
Equivocal			2 (4.1)	-	-	2 (4.1)
Total		1 (2.0)	2 (4.1)	13 (26.5)	33 (67.3)	49 (100.0)

Figures in parentheses are percentages calculated from the overall total
* In 98 cases appropriateness was not applicable. It was only applicable if DRE was suspicious of PCa or equivocal
1= definitely not appropriate, 2= probably not appropriate 3= probably appropriate, 4= definitely appropriate.

Table 8.3 Variation in suspicion of PCa between DRE done in the clinic and DRE done under general anaesthesia in a Lothian sample of patients[a]

Clinic DRE suspicion	General anaesthesia DRE suspicion of cancer					
	DS[1]	PS[2]	Equivocal	PNS[3]	DNS[4]	Total
Definitely suspicious	4 (16.7)	-	-	-	-	4 (16.7)
Probably suspicious	2 (8.3)	-	-	-	-	2 (8.3)
Equivocal	-	-	-	-	-	-
Probably not suspicious	-	-	-	-	1 (4.2)	1 (4.2)
Definitely not suspicious	3 (12.5)	1 (4.2)	-	1 (4.2)	12 (50.0)	17 (70.8)
Total	9 (37.5)	1 (4.2)	0 (0)	1 (4.2)	13 (54.2)	24 (100.0)

Figures in parentheses are percentages calculated from the overall total
1= definitely suspicious 2= probably suspicious 3= probably not suspicious 4= definitely not suspicious.
a Note that this is restricted to patients with just one clinic DRE

Table 8.4 Variation in suspicion of PCa between the overall code for two DREs done in the clinic and DRE done under general anaesthesia in a Lothian sample of patients

Clinic DRE code	General anaesthesia DRE suspicion of cancer					
	DS[1]	PS[2]	Equivocal	PNS[3]	DNS[4]	Total
Definitely suspicious	4	-	-	-	1	5(50)
Probably suspicious	1	-	-	-	1	2(20)
Equivocal	2	-	-	-	-	2(20)
Probably not suspicious	-	-	-	-	-	0(0)
Definitely not suspicious	-	-	-	-	1	1(10)
Total	7(70)	0(0)	0(0)	0(0)	3(30)	10(100)

Figures in parentheses are percentages calculated from the overall total
1= definitely suspicious 2= probably suspicious 3= probably not suspicious, 4= definitely not suspicious.

Table 8.5 Variation in suspicion of PCa between the overall code of all DREs done in the clinic and DRE done under general anaesthesia in a Lothian sample of patients

Clinic DRE code	General anaesthesia DRE suspicion of cancer					
	DS[1]	PS[2]	Equivocal	PNS[3]	DNS[4]	Total
Definitely suspicious	8 (23.5)	-	-	-	1 (2.9)	9 (26.5)
Probably suspicious	3 (8.8)	-	-	-	1 (2.9)	4 (11.8)
Equivocal	2 (5.9)	-	-	-	-	2 (5.9)
Probably not susp.	-	-	-	-	1 (2.9)	1 (2.9)
Definitely not susp.	3 (8.8)	1 (2.9)	-	1 (2.9)	13 (38.2)	18 (52.9)
Total	16 (47.1)	1 (2.9)	0 (0)	1 (2.9)	16 (47.1)	34 (100.0)

Figures in parentheses are percentages calculated from the overall total
1= definitely suspicious 2= probably suspicious 3= probably not suspicious
4= definitely not suspicious.

Table 8.6 Histological findings of TURP operation and lesion prostatic biopsy specimens in a Lothian sample of PCa patients

TURP findings	Biopsy findings			Total
	PCa found N (row %)	PCa not found N (row %)	biopsy not done N (row %)	
PCa found	2(1.6) (15.4)*	4(3.1) (100)	122(95.3) (93.8)	128(100) (87.1)
PCa not found	9(90) (69.2)	0(0) (0)	1(10) (0.8)	10(100) (6.8)
TURP not done	2(22.2) (15.4)	0(0) (0)	7(77.8) (5.4)	9(100) (6.1)
Total	13(8.8)	4(2.7)	130(88.4)	147(100)

* figures in these parentheses are column percentages

Table 8.7 Incidental status classification according to tumour pathological extent in a Lothian Sample of PCa patients

Pathological tumour extent	TURINC* group			
	C	Uncertain	Not TURINC	Total
Small extent:	31	-	1	32
Large or unknown extent:	48	5	43	96
TURP not done	-	-	19	19
TOTAL	79	5	63	147

Table 8.8 Incidental status classification in relation to suspicion of PCa by overall DRE in a Lothian sample of patients

Overall DRE suspicion	TURINC* group			
	TURINC	Uncertain	Not TURINC	Total
Definitely suspicious	1	-	29	30(20.4)
Probably suspicious	-	-	17	17(11.6)
Equivocal	-	1	1	2(1.4)
Probably not suspicious	17	-	3	20(13.6)
Definitely not suspicious	59	-	5	64(43.5)
No valid DRE	2	4	8	14(9.5)
Total	79(53.7)	5(3.4)	63(42.9)	147(100.0)

* TURINC = TURP-detected incidental

Table 8.9 Incidental status classification in relation to bone metastasis in a Lothian sample of PCa patients

Bone scan results	TURINC* group			
	TURINC	Uncertain	Not TURINC	Total
Positive for metastasis	-	-	21	21
Negative for metastasis	32	3	20	55
Done but late**	25	2	13	40
Not done	22	-	9	31
Total	79	5	63	147

** Bone scan was done more than 2 months after diagnosis

Table 8.10 Number and percentage of TURINC* and NOT TURINC cases classified in a sample of PCa patients from Lothian by year of registration

Incidental status classification	Year of registration					
	1982-84		1988-90		1982-90	
	N	%	N	%	N	%
TURINC	30	**39.5**	49	52.7	79	**46.8**
NOT TURINC	27	**35.5**	36	38.7	63	**37.3**
Unclassifiable	4	**5.3**	1	**1.1**	5	**3.0**
Total	**76**[a]	100	**93**[ab]	100	**169**[ab]	100

a 22 case notes were missing or inadequate (15 in 82-84 and 7 in 88-90)
b 3 cases excluded for lack of evidence of primary disease
* TURINC = TURP-detected incidental

Table 8.11 Estimated numbers and percentages of TURINC* and NOT TURINC cases of PCa in Lothian by year of registration

Incidental status	Year of registration				absolute & % increases	
	1982-84		1988-90		82-90	
	N	%	N	%	N	%
TURINC						
Minimum	31	7.6	56	13.0		
Average	39	9.6	59	13.7	20	51.3
Maximum	48	11.8	63	14.6		
NOT TURINC						
Minimum	359	88.2	368	85.4		
Average	368	90.4	372	86.3	4	1.1
Maximum	376	92.4	375	87.0		
Total	407	100.0	431	100.0	24	100.0

* TURINC =TURP-detected incidental

Table 8.12 Estimated numbers and truncated crude rates (per 100,000 men-years) of TURINC* and NOT TURINC cases of PCa in Lothian
by year of registration

Incidental status	Year of registration				Total		% Change
	1982-84		1988-90		82-90		in base rates
	N	Rate	N	Rate	N	Rate	82-90
TURINC							
Minimum	31	14.4	56	26.4	87	20.3	83.3
Average	39	18.1	59	27.8	98	22.9	53.6
Maximum	48	22.2	63	29.7	111	25.9	33.8
NOT TURINC							
Minimum	359	166.3	368	173.5	727	169.9	4.3
Average	368	170.4	372	175.4	740	172.9	2.9
Maximum	376	174.2	375	176.8	751	175.5	1.5
Total No. of cases	407	188.5	431	203.2	838	195.8	7.8
Target population	215900		212123		428023		

* TURINC =TURP-detected incidental

Figure 8.1 Selected sample of prostate cancer cases in Lothian by time interval from diagnosis to bone scan examination

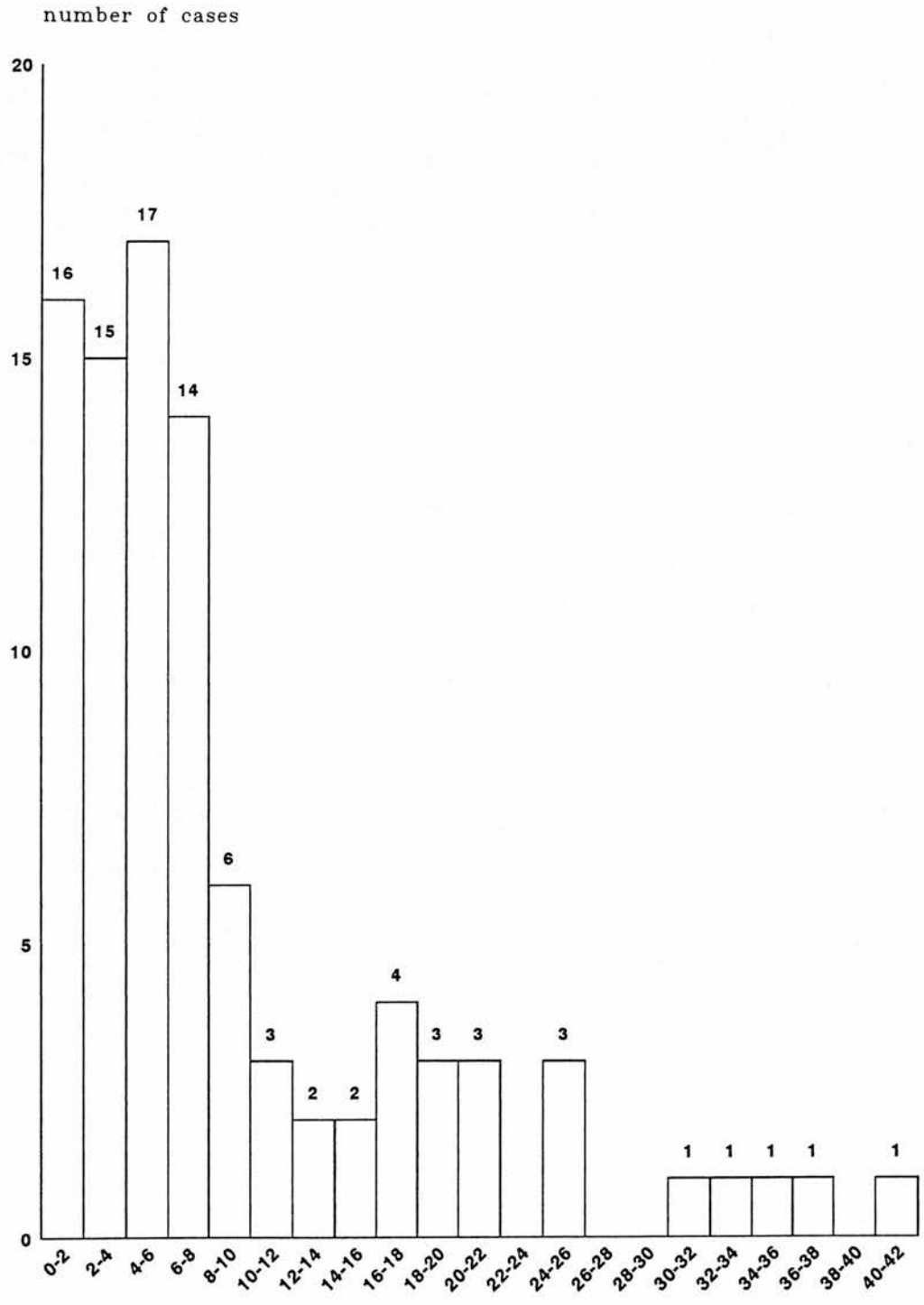


Figure 8.2 Selected sample of prostate cancer cases in Lothian by time interval from diagnosis to clinical T-staging

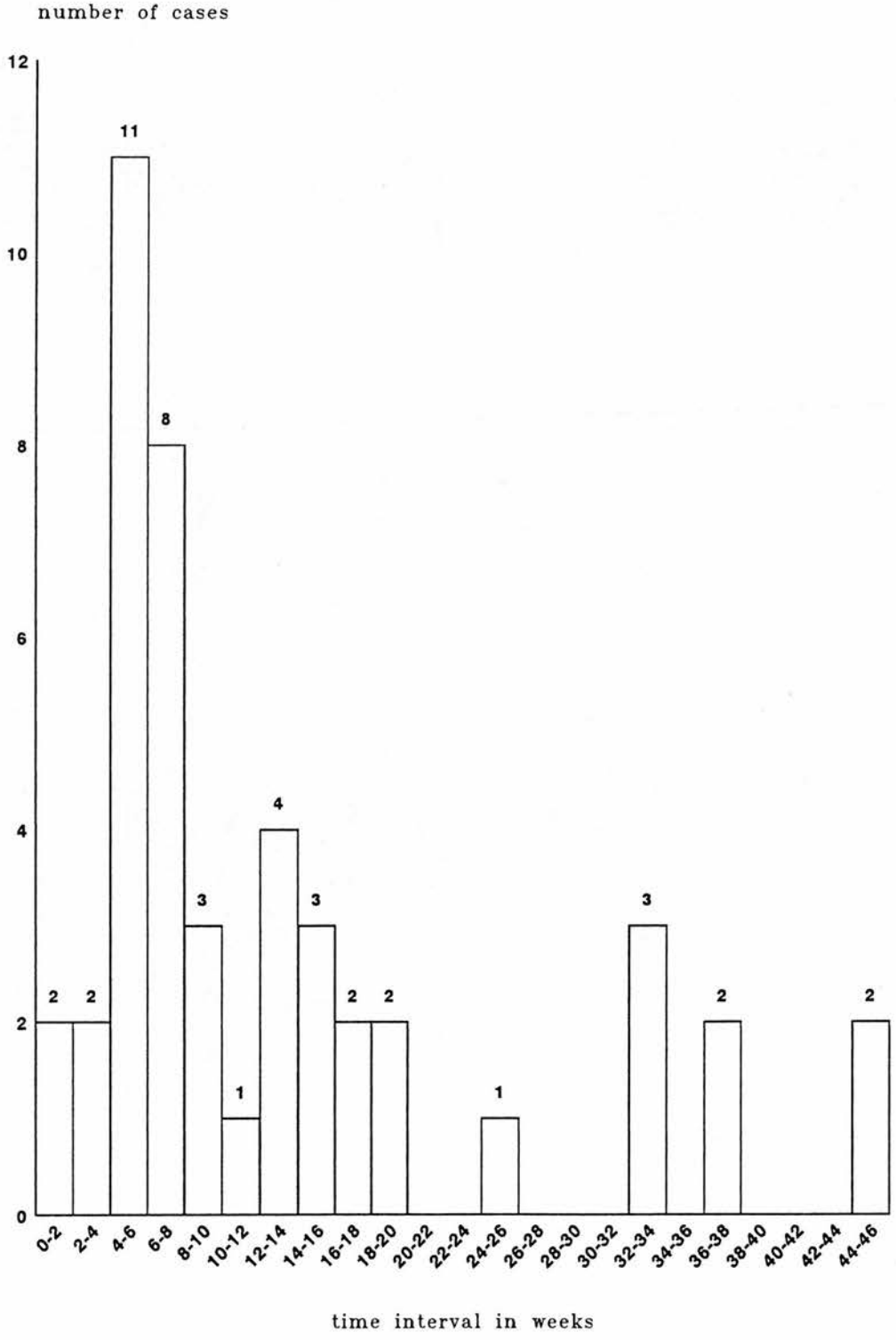
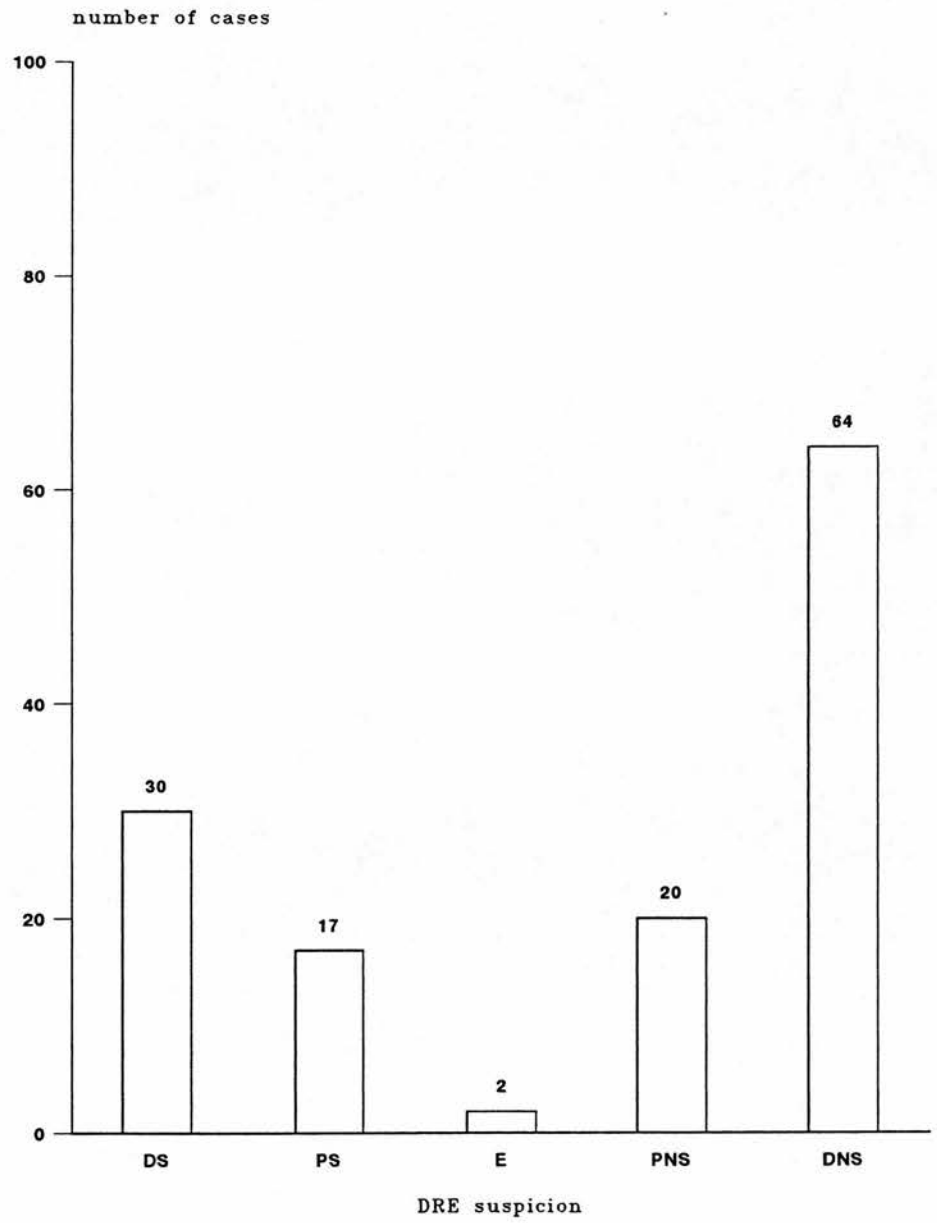
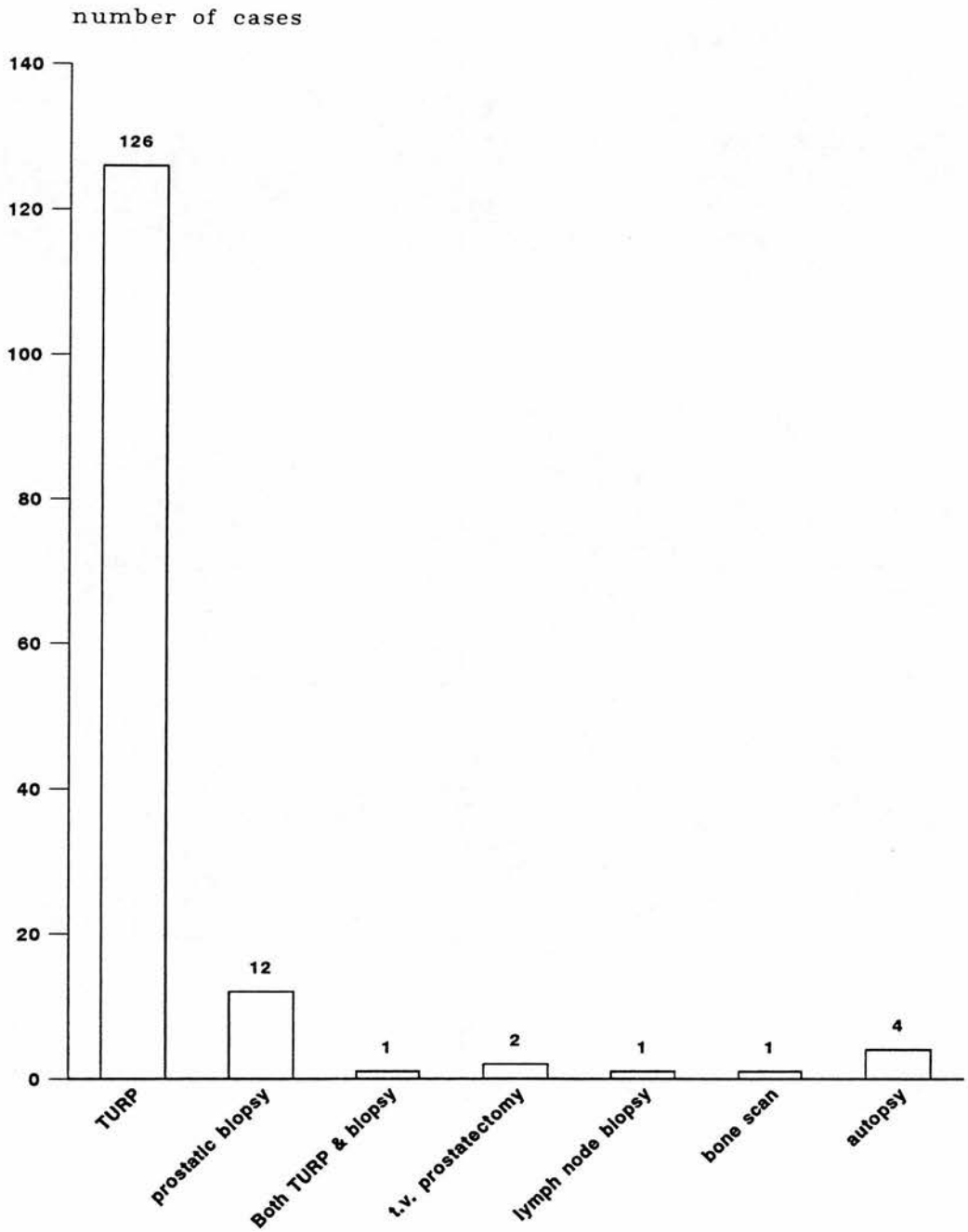


Figure 8.3 Overall digital rectal examination suspicion of prostate cancer in a Lothian sample of patients



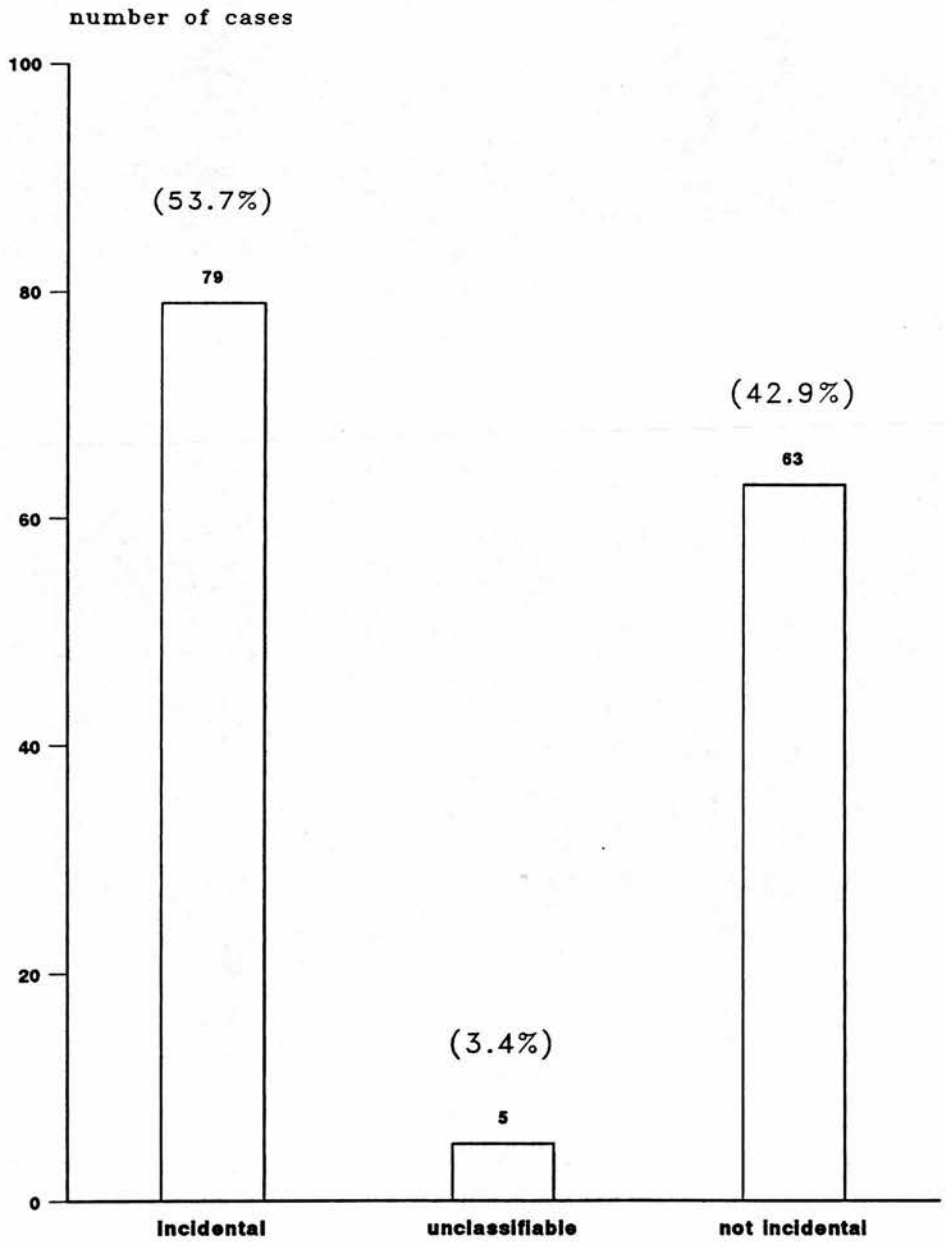
DS=definitely suspicious, PS=probably suspicious, E=equivocal,
PNS=probably not suspicious, DNS=definitely not suspicious
N.B. 14 cases have no valid DRE

Figure 8.4 Method of diagnosis in a Lothian sample* of prostate cancer patients



* This was a selected sample based on certain criteria

Figure 8.5 Incidental status in a sample* of prostate cancer patients in Lothian



* This was a selected sample based on certain criteria

4. DISCUSSION

4.1 Record and Data Availability

Out of 172 case notes selected, 147 were successfully reviewed but 22 (12.8%) were either not available (15) or inadequate for urologic data (7). The problem of missing or incomplete records is not unexpected in retrospective case note reviews. In a recent study on accuracy of Scottish 1990 cancer registration data, 8% of the case notes were not available (Brewster et al, 1994). West (1976) reported on 19% missing rate in his study of accuracy of cancer registration in South Wales. What is peculiar in this study however, is its inclusion of cases diagnosed more than ten years in the past and proportionally more notes were missing among those cases compared to those diagnosed in the more recent years of the study.

Patient's death was assessed by Gulliford et al (1991) in their study on evaluation of non-response, and was found to be a significant determinant of patient's case note unavailability. Availability of hospital patients' notes is also affected by patients movement between different residences and treatment centres, and to allow for this, some of the records have been successfully chased at hospitals other than those originally coded.

Missing cases are a potential source of selection bias that may undermine the validity of the results in epidemiologic studies and, that is when the characteristics under study differ between the available and missing cases. Determination of the amount and direction of this bias is not always possible. In the present study some assumptions made about the characteristics of missing cases in the estimation of incidental cases counts provided a reasonable solution to the problem.

Some of the available records were incomplete for data items such as DRE and bone scan examination results, that are crucial for classifying cases according to their incidental

status. In some of the cases these procedures have been performed but too late after diagnosis to be relevant. Given the distribution of bone scan and T-staging over time (Figure 8.1 and 8.2), a cut off point at 2 months after diagnosis was selected to distinguish valid procedures (those that are likely to apply at the time of diagnosis) from invalid ones. This two-month rule has been applied by an American Cancer Registry to determine the relevance of a case investigation and staging information to the diagnosed tumour (Geralch et al 1987), and while this period allows for any possible delay till the investigations are done, especially those investigations requiring transfer of patients to a central facility (Radiation Oncology Department at the Western General Hospital of Edinburgh), it is also short enough to be unlikely to affect disease progression.

There were only 14 cases who had no valid DRE, 10 (77.9%) of which were successfully classified according to their incidental status (Table 8.8). Similarly in the case of bone scan where nearly half of the available cases (71/147) had no valid bone scan results (not done or done late), only 2 of these were unclassifiable (Table 8.9). However, in those cases without valid bone scan, but classifiable, the bone scan results were important for their classification as definite or probable. Some of those with late bone scan examinations were negative for metastasis.

It could be argued then that these cases were metastasis-free at diagnosis and this information therefore, can be used to classify them. However, they were excluded to maintain consistency with the 2-month period which was applied to those with late positive bone scans.

4.2 DRE Interpretation

Interpretation of DRE is hampered by variability in the examiner's impression. Digital rectal examination is highly subjective, depending on the examiner's experience (Cupp and Oesterling 1993). Therefore, variation between examiners in malignancy suspicion is anticipated. According to Varenhorst et al (1993) there is a good agreement between a urologist and a general practitioner in some of palpatory characteristics of malignancy in 933 patients both of them have examined, and the highest was for nodularity. Yet, the overall agreement in DRE findings in general, as they reported, was 46.5%, and the urologist were 10% higher than the general practitioner in accurately predicting malignancy (positive predictive values are 0.38 against 0.28). Smith and Catalona (1995) have studied the agreement between faculty and resident urologists in classifying DRE findings (benign versus suspicious) in 116 volunteers with 8% prevalence of cancer. Their results, based on Kappa statistics show that agreement in suspicion of cancer on DRE was only fair among urologists (k=0.22), and this agreement differs by urologist's experience.
In the present study DRE's done by general practitioners were excluded; however, uncertainty and variability in DRE findings have still been encountered. There was one case in which findings could not be interpreted and in another the findings of two DREs were contradictory so that their overall DRE findings were equivocal (Figure 8.3). Including this later case, major disagreement between DREs done in the clinic and under general anaesthesia was noticed in a total of 6 out of 34 cases (17.6%) with available multiple DREs (Table 8.5).

Variation between the two examinations can be influenced by several factors. Generally, DRE is more reliable when it is done under g.a. than in the clinic (Babayan 1989). In the present study most patients (107) did not have a DRE done under g.a., and

had this missing information been available it could have affected the incidental status, most likely by detecting some cancer cases that were missed by a clinic DRE and thus reducing the number of cases designated as TURINC.

Inclusion of some DREs done more than 2 months prior to diagnosis could mean that DRE variability was attributable to a true change in the disease extent with time, but the number of such cases in the DRE comparison was only 4.

Intra-observer and inter-observer bias can always be part of the DRE variability, especially the latter (Varenhorst et al, 1993; Smith and Catalona, 1995), but this cannot be assessed from this study. Interpretation of DRE suspicion of cancer from the case notes, by the investigator, could also be a potential cause of the variation which was minimised in this study by using standard classification of DRE findings and interpretation (see appendix D).

Having said that, the Kappa statistic value of 0.62 for the present data (Table 8.5) indicates good agreement, according to the classification of levels of agreement by Smith and Catalona (1995).

A key issue in the DRE variability is the relatively low specificity and sensitivity of DRE criteria for malignancy, which as correctly described by Kaufman et al (1954), are difficult to standardize. Some benign conditions, like calculi and chronic inflammatory disease may be mistakenly diagnosed as malignancy (Shah 1989, Prout 1973). The evidence from the study of Jewett (1956) is crucial here, where 50% of suspicious nodules in his series proved to be benign on biopsy. On the other hand, presence of cancer may be overlooked especially if it causes no deformity in the outline of the gland (Chisholm 1986). Stamey et al (1993b) have reported very large incidental carcinomas in which carefully done DRE revealed diffusely enlarged prostates consistent with BPH.

For these reasons, the DRE suspicion of cancer in this study was validated for its appropriateness to the diagnosed tumour by histological verification of the lesion and its extent at subsequent biopsy or examination of TURP specimen. It is interesting to note that none of the cases with small extent tumours had suspicious DRE, and while all probably suspicious DREs were appropriate, only 1 out of 30 definitely suspicious DREs was followed by negative biopsy (Table 8.2). Assessing DRE for false negative results was done by taking any mention of T3+ or suspicious DRE up to 2 months after diagnosis, as an indication of clinically manifest cancer even if DRE was not suspicious before diagnosis (see appendix D). Although post-diagnosis T-staging and DRE could be influenced by diagnosis, suspicion of cancer by DRE, especially if part of the prostate has been resected already, is a sign of significant extent, and if tumour was found to be T3 stage two months after diagnosis it would be unlikely that it had been T1 before diagnosis.

Translation of an examiner's written impression to determine whether DRE is suspicious of cancer was difficult in this study unless the diagnosis of malignancy or no malignancy was spelt out by the examiner. Otherwise, the decision of the investigator may carry the risk of subjectivity. To minimize this investigator misclassification bias and to ensure consistency in his judgement on DRE findings, coding of suspicion of malignancy was done according to pre-set criteria (see appendix D) and a five-point scale with some flexibility in determining whether the case should be definite or probable in either of benign and malignant diagnoses.

It is worthwhile to note here that none of the cases had been examined by transrectal ultrasound (TRUS), although it is now widely used in the United States, in particular, to guide biopsy (Mettlin et al 1993). This is undoubtedly related to its cost (Chisholm 1986) and its poor performance in the early attempts (Okafor et al 1983). Prostate specific

antigen has not been considered in this study, as it had rarely been used at the time of the study.

4.3 Incidental Classification

The main issue in this study is the classification of cases, according to the way they were detected, to distinguish those that are likely to be incidental and TURP-detected PCa. There were 79(53.7%) cases in the study which fulfilled the pre-specified criteria. They were subdivided into definitely incidental (24) and probably incidental (55).

The results show that classification of TURP-detected incidental (TURINC) cases from case notes is possible, but time consuming, with only a few , 5 cases(3.4%), not classifiable. Yet, reliability of this classification depends upon accuracy of the data and their interpretations and the criteria used to define the incidental groups. The definition of TURP-detected incidental (TURINC) PCa followed here is more conservative than its definition in the TNM classification of tumours. While the TNM classification considers findings at the time of diagnosis (Schroeder et al 1992), this study has allowed for findings up to two months after diagnosis to rule out any chances of missing or underestimating the clinical evidence of tumour at diagnosis. Definition of TURINC cases was further restricted by excluding those with positive metastasis on bone scan. Presence of 47 cases without valid bone scan results (22 had no bone scan done and 25 had a bone scan done but late) in the TURINC group (Table 8.8) represents a potential weakness in the classification. However, while these cases were all classified as probably TURINC 13 out of the 22 cases without bone scan had small extent tumour and thus, have only 2% chance of having progressed, according to Cantrell et al (1981). Besides, urologists will often postpone the bone scan for what they believe to be an incidental non-aggressive tumour, until further developments i.e. recurrence or exacerbation of symptoms. Of the 25 cases,

in which a bone scan was done but irrelevant (done more than two months from diagnosis), 22 were negative even after this time, which supports their classification. This shows that although these cases were assigned to the "probably TURINC" group, 22 of them would have been "definitely TURINC" if an earlier bone scan had been done. However, there are 12 cases (9 without bone scan and 3 with a bone scan done late) whose impact on the classification remains uncertain.

Another potential threat to the reliability of the classification could be the problem of accuracy of pathological tumour extent assessed from TURP specimens. The only area in the study in which tumour extent has been used was the assessment of appropriateness of DRE suspicion. Out of 31 cases with small extent tumour in the incidental group only 2 cases were affected by this criterion and as they had no valid appropriate DRE they were classified as TURINC. Accuracy of this judgement could be questioned owing to the possibility that with TURP some residual tumour may be left in the un-resected part of the prostate. This deficiency in staging TURP specimens cannot be corrected by a second-look TURP (Parfitt et al 1983) especially that it is short of reaching residuals of the peripheral zone (McNeal et al 1988a); proper tumour extent assessment can only be achieved by radical surgery (Benson and Olsson 1989).

Given all of these difficulties in data interpretability, the classification of incidental PCa from the patients' case notes was possible. Out of 172 cases in the sample about 85% (142) have been classified (Table 8.10). A single observer (the investigator) looked at the data for both times so the temporal comparisons should not be influenced by bias from policy decisions.

4.4 Estimated total number of incidental cases in Lothian

The estimated proportional registration ratio of TURP-detected incidental cases in Lothian shows that they represent a relatively small proportion (11.7% on the average) of the total registered cases. However, their PRR has increased and they can account for most of the increase in the total registered cases (Table 8.11). Their crude incidence rate has increased by 53.6%, compared to that for other cases which has increased by only 2.9% (Table 8.12). The small increase in the incidence of other cases can largely be attributed to ageing of the total population between the two study periods. So most of the total increase in the age-adjusted data can be explained by the increase in the number of TURP-detected incidental cases.

These findings are consistent with the dramatic rise in the number of TURP operations performed for BPH treatment in Scotland during the same period (Duncan and Garraway 1993), and with the findings of Potosky et al (1990) who reported a strong correlation between the PCa incidence and TURP operation rate in the United States.

The validity of our findings could depend, *priori*, on the validity of the assumptions made about the missing and unselected cases. But, the probabilities of being TURINC applied to the missing cases provided a range within which the true value of this probability lies.The average estimate arrived at by classifying the missing cases according to conditional probabilities applied to groups defined by SMR1 data have been found to be the best available indicators of "TURINC" probability. Cases that have not been sampled (636 cases) are very unlikely to be TURINC cases because they have no SMR1 for BPH. Our estimates, therefore, represent the best possible quantification of the number of TURP-detected incidental prostate cancer cases among men in the age of 55-79 in Lothian in 1982-84 and 1988-90 from case notes clinical data now available.

CHAPTER IX

THE TREND IN INCIDENTAL PROSTATE CANCER AND ITS CONTRIBUTION TO THE TREND IN THE TOTAL REPORTED INCIDENCE

1. INTRODUCTION

The likely contribution of TURP-detected incidental PCa cases to what is believed to be all or partly an artefactual increase in prostate cancer reported incidence is well appreciated among scientists. In an article entitled "The rise in prostate cancer incidence a fact or a myth", Alexander and Boyle (1995) conclude that, after allowing for a small part that is due to ageing, nearly all the increase in the incidence in Europe between 1970-72 and 1985-87 can be explained by increased detection of TURP-detected incidental cases. Wilson (1987) attributed the increase in the reported incidence in Scotland between 1963 and 1982 to the incidental cases, among other factors. Chisholm (1986) writes on the epidemiology of the disease and ascribes the change in its incidence to the increase of detection of these cases.

In the year 1990, Potosky and his colleagues from the United States presented evidence for this association using an ecologic study design. They showed that 88% of the increase in the total incidence rate of prostate cancer in the United States during 1974-1986 could be explained by the increase in the rate of TURP performed for the treatment of benign prostatic disease. Caution is required since this type of study design is based on grouped data analysis so that the relationship between the two correlated variables may not hold at the individual level, and that this relationship may in part be explained by the effects of confounding variables (Esteve et al 1994).

An upward trend in the number and percentage of prostate cancer cases identified first by TURP done for BPH has been reported by Corder et al (1994) following a review of medical records of 897 PCa cases diagnosed in Rochester (USA) from 1935 to 1989.

In Scotland, such evidence on the contribution of the TURP-detected incidental cases to the total prostate cancer trend has not been presented yet, but, as in many other countries, the rate of TURP operations done for treating BPH increased during the late seventies and the eighties (chapter VI; Duncan and Garraway, 1993) and this must have contributed cases to the total reported incidence of prostate cancer.

Classification of cases and estimation of the probability of cases being incidental in Lothian has been carried out by reviewing a sample of case notes of prostate cancer cases that were diagnosed in the region and were, from routinely recorded data, possibly incidental (Chapter VIII). In this chapter, the trend of the absolute number of TURP-detected incidental PCa cases in Scotland will be estimated by applying the probabilities of being incidental for subsets of cases (defined by routinely collected information) calculated from the Lothian sample to the national data of PCa registration. This will provide the basic data required for breaking down the reported incidence into two components; the incidentally-found and the clinically-apparent cases, and thus quantifying the amount of change in the disease incidence that is due to the increased detection of the incidentally-found cases.

2. METHODS

2.1 Estimating unconditional probabilities of TURP-detected incidental (TURINC) PCa

The following systematic procedure has been adopted to estimate the unconditional[1] probability that a case of PCa (registered with SMR6 or with an SMR1 for PCa) was incidentally found. These probabilities are specific to age-group (<65, ≥65) and to time period 82-84, 85-87, 88-90. They require the following assumptions:

(a) Cases without an SMR1 record mentioning BPH will not be incidental

(b) Probabilities of being TURP-detected incidental (TURINC) PCa conditional on the SMR-incidental-key group are the same for all time periods and for the rest of Scotland as for Lothian.

2.1.1 Step 1: Distribution of SMR-incidental probability groups

These were derived for each of the two age-groups (35-64, 65+ years) and the three time periods (82-84, 85-87 and 88-90) using the SMR-incidental probability groups defined in chapter VIII with a slight modification: the 3rd and 4th groups were amalgamated here in group 3 and group 0 was added for cases which lacks an SMR1 for BPH, and thus cannot be incidental, as illustrated in table 9.1.

[1] Without conditioning on SMR1 data

Table 9.1 Distribution of cases by age and SMR-incidental groups

patient's age at diagnosis	SMR-incidental (SMRINC) probability groups				Total cases
	1	2	3	0	
55-64 years	n1,1,j	n2,1,j	n3,1,j	n0,1,j	n+,1,j
65-79 years	n1,2,j	n2,2,j	n3,2,j	n0,2,j	n+,2,j
Total	n1,+,j	n2,+,j	n3,+,j	n0,+,j	n+,+,j

j=1,2,3 for 1982-84, 85-87 and 88-90

2.1.2 step 2: Allocation of probabilities conditional on the SMR-incidental probability group

These have been taken from the Lothian sample. Thus,

Pr(TURINC | SMR-incidental group=1) = $p_k = p_1 = 0.909$

Pr(TURINC | SMR-incidental group=2) = $p_2 = 0.455$

Pr(TURINC | SMR-incidental group=3) = $p_3 = 0.391$

Pr(TURINC | SMR-incidental group=0) = $p_0 = 0.00$

Lower and upper 95% confidence limits for p_1 - p_3 have been taken as $p_k \pm 1.96[p_k(1-p_k)/n_k]^{½}$ Where n_k is the total number of cases in group k (over 1982-90). The probability of being TURINC for any case in group 0 is zero according to the assumption 2.1.a above.

2.1.3 Step 3: Correction factor estimation

The correction factor (C) is a constant used in order to allow for the difference between the number of incidental cases estimated using best available data from the case notes (best estimate or E_1) relative to their estimate from the routine SMR data (average estimate or E_2).

The use of this factor is based on the assumptions that;

(a) It is age-specific,

(b) It is the same for Lothian as for other Scottish regions, and

(c) It does not change with time.

The factor was obtained by taking the ratio of the best estimate (E_1) of these cases in the Lothian sample calculated in chapter VIII, and an average estimate (E_2) among them obtained using their routine SMR data.

The method of obtaining E_1 has been explained in chapter VIII starting on page 123, and E_2 was derived for each age-group by the equation $(E_2)_i = \Sigma_k n_{i,k} \cdot p_k$ where,

$n_{i,k}$ = number of PCa cases in the ith age-group and kth SMR incidental-key group of the Lothian sample, and i=1,2 and k=1,3
p_k= probability of TURINC in kth SMR incidental-key group of the sample

2.1.4 Estimated unconditional probabilities

The SMR-incidental probability groups form a partition of the sample space. Thus the unconditional probability for age-group i, for time period j of being TURP-detected incidental can be obtained from the conditional probabilities as

$$\Pr(\text{TURINC}) = p_{ij} = \Sigma_k \, p_k \cdot C_i \cdot n_{k,i,j}/n_{+,i,j}$$

Point estimates of p_{ij} have applied this formula to the p_k's and upper/lower bounds have applied it to upper and lower confidence limits for the p_k's. These three are referred to as middle, upper and lower estimates of the (unconditional) probability that a case was TURP-detected incidental PCa. As implied from 2.1.2, p_{ij} will be zero for cases in SMR-incidental group 0 (since their p_k is zero).

2.2 Estimating the absolute number and rate of incidental PCa

2.2.1 The age-specific values of the unconditional probability of being incidental (middle, lower and upper) have been applied to the reported registrations of PCa for Scotland, stratified by period and age, to obtain middle, lower and upper age-period-specific estimate of the count of TURINC cases as follows: $n_{i,j} = p_{i,j} \cdot N_{i,j}$ where

$n_{i,j}$ is the number of TURINC cases in i age-group and j period,
$N_{i,j}$ is the total number of reported cases in that age-group and period.

2.2.2 For calculation of absolute numbers of cases and crude and age-adjusted incidence rates, age was classified into 9 groups; 35-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85 or higher. The unconditional probability of being incidental ($p_{i,j}$) calculated for the younger group was applied to cases below 65 and the one calculated for the older was applied to cases older than 65. For each period, the total number of TURINC cases is the sum of the numbers over the age subgroups.

2.2.3 Age-specific incidence rates were calculated for the age-groups; 35-49, 50-59, 60-69, 70-79 and 80 or higher. The number of cases in each of these age-groups is the sum of cases in the smaller groups within the range.

2.2.4 Age-specific and total numbers of clinically-apparent cases in the reported PCa series were derived by subtraction (total reported minus estimated TURINC cases).

2.2.5 Age-specific, three-year average incidence rates for TURINC and clinically-apparent cases were calculated for the estimated population of males in Scotland published in the annual report of the registrar general (Rgistrar General Scotland 1982-1990). Rates were then adjusted for temporal changes in age-structure of the population by direct-standardization using the 1988-90 population as a standard. This

will remove the effect of the changes in the age-structure of the population from the trends of the incidence rates.

2.2.6 The rate of change in the age-specific and age-adjusted rates of TURP-detected incidental and clinically-apparent PCa for a specific period was calculated as a percent increase from the base-year (1982-84) rate.

2.3 Analysis of components of the trend in the reported incidence

The trend in the incidence of PCa between 1982-84 and 1988-90 was analyzed for its components. One, which may be considered artefactual, includes the effects of ageing, improved completeness of reporting and increased reporting of incidentally-found cases (TURP-effect). The method used for that here is analogous to that of Devesa and Schniederman (1977) for components analysis of the cancer mortality trend. The starting point in the analysis is the reported registrations of PCa in the first study period of 1982-84 (N_1), and the end point of it is the reported registrations in the final period of 1988-90 (N_2).

The total change in incidence between these two periods is equal to the excess in registrations of 1988-90 over those of 1982-84 ($N_2 - N_1$). Contribution of each of the components mentioned earlier to this total change has been derived as follows:

2.3.1 Effect of ageing

Age-specific incidence rates for registrations reported in 82-84 were applied to 88-90 estimated male population in Scotland. The resulting total number of cases is that expected after the change in the population (N_3) while keeping the age-specific incidence rates unchanged. So, the number of cases in N_2 that is attributable to ageing is equal to N_3-N_1. Of N_2, the difference N_2-N_3 will remain to be explained.

2.3.2 Effect of improved completeness of reporting

This was obtained by applying the percentage increase in the reported age-adjusted incidence that is attributable to completeness (K), which has been estimated in chapter VII at 4%, to N_3 to yield N_4, so that $N_4 = N_3 * (1+K)$. Accordingly, the number of cases in N_2 that is attributable to completeness is equal to N_4-N_3 and, N_2-N_4 remains for explanation.

2.3.3 Effect of increased detection of incidental cases by TURP (TURP-effect)

After adjusting the reported incidence rates of TURINC and total cases of 1982-84 for age[1], the percentage increase (r) in the total expected cases in 1982-84 (T_1) that is explained by the increase in the number of estimated TURINC cases from n_1 in 82-84 to n_2 in 88-90 is equal to the excess in n_2 over n_1 divided by T_1 x 100.

Three values for each of n_1 and n_2 have been obtained corresponding to those for the probability (P(incidental)) and therefore, three values were derived for r. The resulting r values were applied to N_4 above to obtain N_5, after allowing for TURP, where $N_5(\text{lower, upper, middle}) = N_4 * (1+(r/100)_{l,u,m})$.

The number of cases in N_2 that is attributable to increased TURP-detected incidental cancer cases is equal to N_5-N_4. The remaining part (N_2-N_5) is yet to be explained and represents the additional cases due to the component of the trend which is attributable to genuine increase in disease burden (or not-examined artefacts).

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[1] Age was adjusted by directly standardizing rates to 1988-90 population.

3. RESULTS

The relative distribution of prostate cancer cases registered during 1982-90 in Scotland among "SMRINC" probability groups is shown in table 9.2.

Table 9.3 shows a trend in the probability of incidentally-found PCa among the reported cases in Scotland in 1982-90 classified by age and year of registration. Cases less than 65 years of age have lower probability of being incidental than the older cases (5.6 versus 8 per cent in 1982-84 and 9.4 versus 12.2 percent in 1988-90). This estimates that the probability of being incidental among the younger cases has risen by 68.2 percent, and the rise among older cases was less steeper at 52.4 percent. The lower and upper limits of the probability are shown in parentheses in table 9.3.

The time trend in the crude and the age-specific reported incidence rates of incidentally-found cases, and the total percentage change in the base-year rates with time are shown in table 9.4. The crude rate has increased from 3.2 per 100,000 men in 1982-84 to 5.8 in 1988-90; a total increase of 81.3 percent. Age-specific rates have all increased but the increase was higher in the lower age-groups; it doubled for cases in the age-group 50-59 years and increased by 84, 69.7 and 67.9 percent in the following age-groups in descending order.

Crude and age-specific reported incidence rates of clinically-apparent cases are much higher than the rates of incidentally-found cases, but the total percentage increases in base-year rates were much lower among them (Table 9.5). The crude rate has increased by a total of 13.4 percent, from 38.2 per 100,000 men in 1982-84 to 43.3 in 1988-90 (compared to 81.3 percent increase in incidentally-found crude rate).

The total percentage increase in age-specific rates ranges from 87.5 percent for cases in the lowest age-group to 5.3 percent for those in the highest age-group

(corresponding range for incidentally-found cases is 100 - 67.9). An exception to the downward trend in the total percentage increases is the 6.8 percent for the age-group 50-59 years, which is lower than that for the next higher group (10.9 percent).

After adjusting crude incidence rates for age, a total of 10.7 percent increase has been recorded for the age-adjusted rate of total reported cases between 1982-84 and 1988-90 (Figure 9.1). The percentage increase in the age-adjusted rate of incidentally-found cases remained significantly high at 70 percent (Figure 9.2) while that of clinically-apparent cases has fallen to 5.7 percent (Figure 9.3).

Analysis of the main components of the trend in the reported incidence of PCa shows that the total number of reported cases in 1982-84 (3087 cases) has increased till 1988-90, by a total of 17.5 percent of which, 6.2 percent is due to change in the age structure of the population, 4.2 percent is due to improving completeness of reporting and 6.0 percent is due to increased reporting of incidentally-found cases (Table 9.6, Figure 9.4). Of the total increase, 1.1 percent remains to be explained and this percentage may lie between 0.1 and 2.2, corresponding to the percentage increase in the lower and upper estimates of TURP-detected incidental cases (Table 9.6).

Table 9.2 Relative distribution of registered prostate cancer patients among SMR-incidental groups 1982-90

SMR incidental probability group	Proportions of all cases by year and Age					
	82-84		85-87		88-90	
	35-64	65+	35-64	65+	35-64	65+
1 High	0.024	0.027	0.06	0.054	0.078	0.055
2 Middle	0.024	0.026	0.014	0.03	0.019	0.028
3 Low	0.102	0.116	0.124	0.133	0.109	0.158
0 Not incidental	0.849	0.831	0.802	0.782	0.793	0.758

Table 9.3 Probability of TURP-detected incidental PCa among the registered cases in Scotland 1982-1990

Age	Period of registration		
	82-84	85-87	88-90
Young (35-64 years)	0.056	0.084	0.094
	(0.041,0.071)*	(0.067,0.101)	(0.076,0.111)
old (65+ years)	0.08	0.113	0.122
	(0.059,0.102)	(0.086,0.139)	(0.094,0.151)

* figures in parentheses are lower and upper limits of probability

Table 9.4 Estimated crude and age-specific reported incidence rate (per 100,000 men) of TURP-detected incidental PCa in Scotland 1982-90

Age (Years)	Period of registration			Total % Change in base-rate
	82-84	85-87	88-90	
35-49	0.0	0	0.2	-
	(0.0,0.1)*	(0,0)	(0.1,0.2)	-
50-59	1	1.5	2	100.0
	(0.8,1.3)	(1.2,1.8)	(1.6,2.3)	
60-69	8.1	12	14.8	84.0
	(5.9,10.3)	(9.3,14.7)	(11.6,18.1)	
70-79	27.7	43.4	47.1	69.7
	(20.3,35.1)	(33.2,53.6)	(36.1,58)	
80+	49.5	76.6	83.3	67.9
	(36.3,62.7)	(58.6,94.6)	(63.9,102.7)	
Crude	3.2	5.0	5.8	81.3
rate**	(2.3,4)	(3.9,6.2)	(4.5,7.1)	

* Rates in parentheses are lower and upper limits calculated using corresponding confidence limits for probabilities

** Crude rate was calculated for the total population base

Table 9.5 Estimated crude and age-specific reported incidence rate of clinically-apparent PCa cases in Scotland 1982-90

Age (Years)	Period of registration			Total % Change in base-rate
	82-84	85-87	88-90	
35-49	0.8	0.5	1.5	87.5
	(0.8,0.8)*	(0.4,0.5)	(1.5,1.5)	
50-59	17.7	16.6	18.9	6.8
	(17.4,17.9)	(16.3,16.9)	(18.6,19.3)	
60-69	105.9	104.5	117.4	10.9
	(103.7,108)	(101.8,107.2)	(114.1,120.7)	
70-79	318.1	341.8	338	6.3
	(310.7,325.5)	(331.6,352)	(327,349)	
80+	568.1	603.8	598.2	5.3
	(554.8,581.3)	(585.7,621.8)	(578.8,617.6)	
Crude	38.2	41.1	43.3	13.4
rate**	(37.4,39.1)	(39.9,42.3)	(42,44.6)	

* Rates in parentheses are lower and upper limits calculated using corresponding confidence limits for probabilities

** Crude rate was calculated for the total population base

Table 9.6 Components of the trend in total reported incidence of PCa in Scotland 1982-90

component	No of cases	Change from N_1	% change in (N_1)
(a) Base-year (N_1)	3087	0	0.0
(b) Change in age structure(N_3)	3277	190	6.2
(c) (b) + Improved reporting (N_4)	3408	321	10.4
(d) (c) + TURP (N_5)	3592 (3560,3624)*	505 (473,537)	16.4 (15.3,17.4)
(e) All components (N_2)	3627	540	17.5
(f) Residual (e)-(d)		35(67,3)	1.1(0.1,2.2)

* Numbers in parentheses are lower and upper limits of N_5 following corresponding percentages of increase in registrations that are due to TURP

Fig. 9.1 Percentage change in age-adjusted incidence rate of total PCa registrations in Scotland 82-90

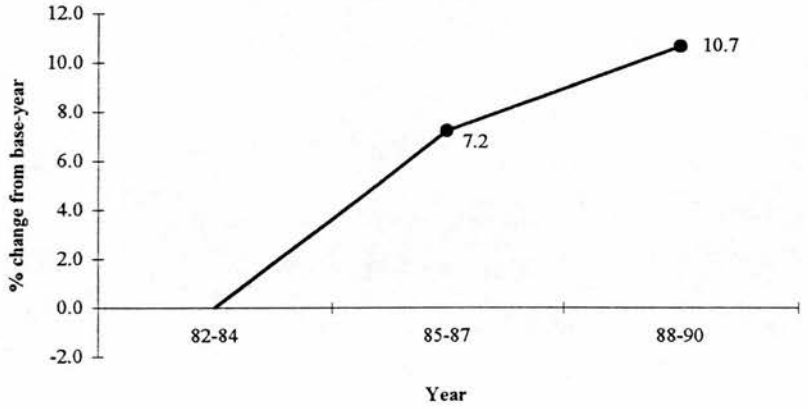


Fig. 9.2 Estimated percentage change in age-adjusted reported incidence rate of incidentally-found PCa in Scotland 82-90

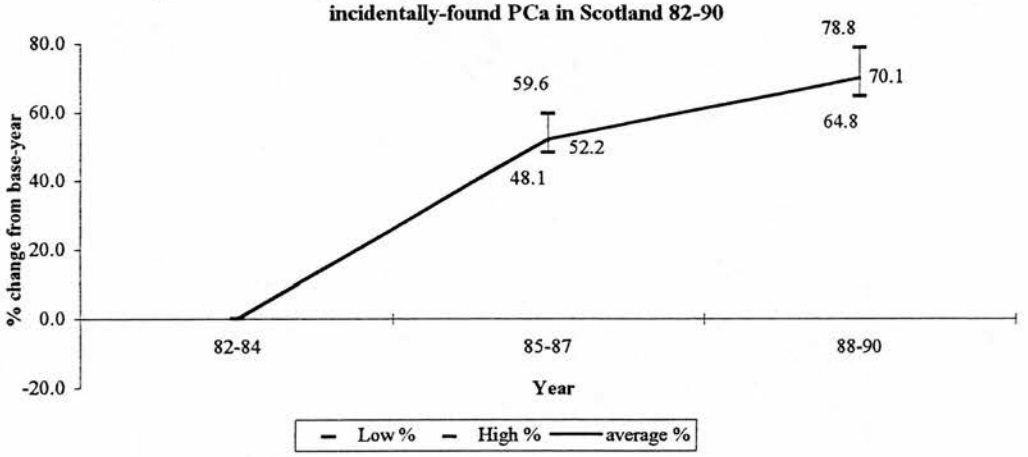


Fig. 9.3 Estimated percentage change in age-adjusted reported incidence rate of clinically-apparent PCa in Scotland 82-90

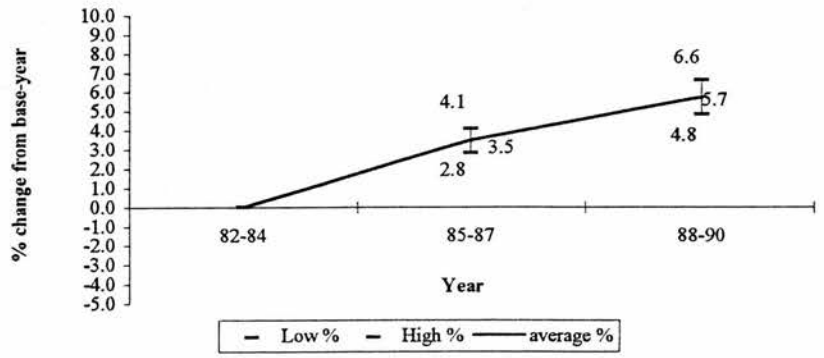
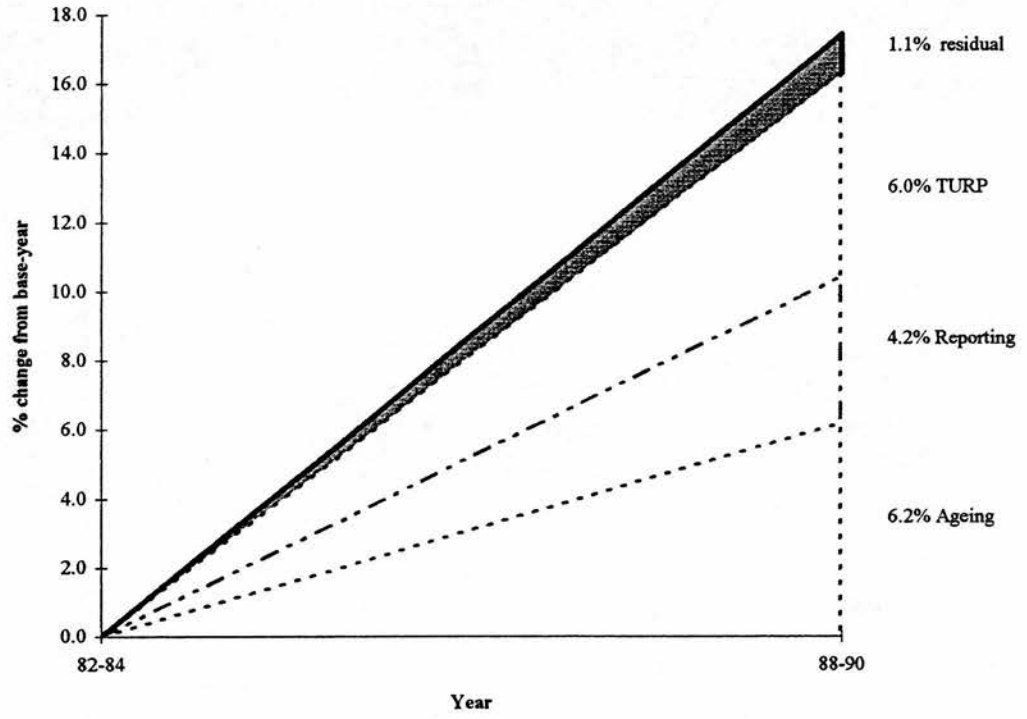


Fig. 9.4 Components of the trend in the total reported incidence of PCa in Scotland 82-90



4. DISCUSSION

The study estimates that about 6 per cent of prostate cancer cases of less than 65 years of age, and 8 percent of older cases reported in Scotland in 1982-84 were incidentally-found after TURP for BPH. These proportional registration ratios (PRR) increased to 9 and 12 percent, respectively, in 1988-90, and the highest percentage ever recorded for any of the two age-groups was 15 percent for older patients reported in 1988-90 (Table 9.2). Rana et al (1993) reported a higher PRR (24 percent) for a series of cases diagnosed in Lothian during the period 1978-1990, however, while it is understood that this series is a selective group of PCa cases, information from other parts of the UK is not available for comparison. The PRR were also lower than this observed in Rochester in the United States (14.2 percent) during 1975-1984 (Corder et al 1994).

On the other hand, clinically progressive PCa has continued to be the vast majority among the reported cases, a pattern which was prevailing in the European countries in the eighties where more than half of the cases presented with metastatic or locally advanced disease (Chisholm 1986; Schroeder 1993). This is slightly different from the pattern in North America where stage A cancer, which is detected mostly by TURP (Potosky et al 1990), accounted for 23 per cent of cases reported in 1974 and 29 per cent of cases in 1990 (Mettlin et al 1993). Nonetheless, the rising trend in PRR (Table 9.2) and the 70 percent increase in age-adjusted rate of incidentally-found PCa (figure 9.3) indicate that a sizeable part of the increase in the total incidence of the disease in Scotland can be explained by these cases which should be considered as an artefact for most purposes.

The increasing trend was more obvious in the younger than older age-groups with the largest increase among patients in their sixties; after ignoring changes in the very young age-group that are based on small numbers.

These trends toward earlier detection and early stage at diagnosis and inclusion of non-progressive disease would explain part of the improvement in survival of PCa patients, observed in Scotland (Black et al 1993), and which has been occurring without any evidence of improvement in treatment. The TURP operation is a major factor in this change not only because of its disclosing of early stage cancers, but also because of the tendency to perform it earlier as has been seen in the higher percent increase in TURP rate among younger patients (Duncan and Garraway 1993). Crucial in these changes also are the greater willingness of patients to seek advice early when they feel alteration in their urinary habits (Chisholm 1986), especially the young (Duncan and Garraway 1993), and the greater physician intention to diagnose the cancer (Wilson 1987).

More striking trends toward early stage and nearly similar age-specific trend have been observed in the United States (Smart et al 1994). However, while TURP for BPH has been implicated in the early eighties changes (Potosky et al 1990), screening for the disease among apparently healthy men, using the prostate specific antigen (PSA) test and transrectal ultrasound (TRUS)-guided biopsy, accounted for these changes in the late eighties, despite the decline in the TURP rate (Potosky et al 1995).

The rise in incidence that is due to increasing detection of incidentally-found PCa (TURP component) is estimated to be 5.4 percent, which, along with its interaction with ageing and reporting components, has accounted for 34 percent (184 cases) of the total increase. This 5.4 percent is quite comparable with the percent increase in

the percentage of cases detected by TURP in USA during 1974-1983, from 54 to 56 percent (Schmidt et al 1986), but very much lower than the 75 percent increase presented by Alexander and Boyle (1995) for the same component, and this is mainly because their estimate is based on an upper extreme value (14 percent) of the percentage of incidental PCa among BPH patients treated with TURP; the average is 10 percent (Sheldon et al 1980). In addition this value will include cases with more extensive disease.

However, the validity of this study's findings and conclusions depend on the validity of extrapolating the incidental probabilities, based on SMR criteria of a case being incidental, for the Lothian region to the whole country. Although this is the only feasible method it need not be accurate. In this study, there is no good reason to believe that incidental probability according to SMR criteria for incidental cases would differ significantly between the Scottish regions. However, the risk of bias due to this extrapolation can not be excluded.

Interpretation of the study results depends also on the reliability of the method dividing the trend into its components. This method is simple and has been followed by Devesa and Schniederman (1977) to analyze components of the trend in cancer-related deaths in the USA.

CHAPTER X

GENERAL DISCUSSION

Prostate cancer has been shown to be an important rising problem in Scotland. The reported incidence rate rose significantly (85 per cent) during the past two decades (1971-1990). The mortality rate rose too but more slowly. Between the highest incidence reported (for the blacks in USA - 100/100,000 population) and the lowest reported rate (Singapore - 4/100,000) Scotland lies in the middle of the range with 48/100000. But, the rise in incidence of PCa is global (Boyle 1997) and the increase in incidence in Scotland is comparable with that in USA (Devesa et al 1995) and other countries (Whittemore 1994).

The question is whether this increasing trend was genuine due to increase in exposure or susceptibility to risk factors or merely, as many scientists believe (Chisholm 1986; Wilson 1987), artefactual due to improvement in reporting efficiency and increased detection of existing, yet not diagnosed, cases. This thesis attempted to address the question and its results, give an answer by describing the trends in two main components of the artefact, reporting efficiency and increased detection of incidental PCa cases, and estimating their contribution to the overall disease trend.

Review of the available Scottish routine data and their secondary analysis results as presented in chapter VI provided some clues to the artefacts in prostate cancer incidence trend by describing the trends in incidence/mortality ratio, the percentage of histologically verified reported cases and the dramatic increase in TURPs for BPH treatment. The hypotheses made from the routine data are consistent with those made by Wilson (1987) and Alexander and Boyle (1995) using similar Scottish data. Similar

suggestions were made by Majeed and Burgess (1994) about the trend of the disease incidence in England and Wales.

Reporting efficiency as assessed in this thesis, by estimating completeness of the Scottish Cancer Registry (SMR6) for PCa cases recorded on the general morbidity database (SMR1) and applying the capture-recapture method, showed some improvement (4 per cent) with time supporting the previous suggestion of its role in the trend of reported disease. It is not unusual for reporting to improve with time (Esteve et al 1994), and while some departure from the precondition of independence of the two databases compared (towards dependence) is possible, the estimated completeness as argued in chapter VII is a good measure of the true completeness for PCa registration in Scotland. However, the hope must be for a better completeness than the present 90 per cent, which is still lower than some European countries (Mattsson et al 1985).

Another major artefact of the trend investigated in this thesis is the increased detection of incidental cases following TURP. In this respect, the thesis presents a unique experience in which routine Scottish morbidity data on SMR1 and SMR6 databases were used to identify and estimate the probability of incidental cases. These probability values were applied to historical data on registered PCa cases to estimate the trend in these incidental cases and their contribution to the overall trend.

This was achieved by first identifying cases from the SMR1 and SMR6 databases for PCa according to SMR criteria available from routine SMR1 data and sampling from them for a fieldwork study. Then, their incidental nature was classified on the basis of the clinical information in patient's hospital case notes. The proportion of cases classified from the case notes as incidental in each group cases specified by

SMR criteria was taken as an estimate of the predictability of a case being incidental given its location in one of the groups defined by SMR criteria (this is assumed not to change with time and over age). From this the unconditional probability for a case being incidental (by age, time) was derived as described in chapter VIII.

Reliability of the classification of cases on the basis of case note information was extremely important for the study because it was acting as a the gold standard on which the predictability of SMR criteria for incidental cases was assessed. Problems encountered were those of missing case notes especially in the early years of the study (1982-84), interpretability and variability of urologists' DRE findings and accuracy of the pathological description of the tumour extent in the TURP specimen. Although their effect cannot be avoided completely, measures have been taken to minimize this by making some assumptions for missing cases about their probability of being incidental, following predesigned criteria for interpreting DRE findings and assuming pathological information is always correct.

Most cases (all but 5) were classified on the basis of case note information. Assuming that this classification is reliable, comparing it with incidental classification based on SMR criteria showed that the latter can correctly identify cases as incidental in 45-90 per cent of the cases depending on the particular SMR criteria group.

Applying these probabilities to Lothian, results were interesting with an increase in the incidental rate that was 18 times the increase in other cases (53.6 versus 2.9 per cent). This shows that a substantial part in the overall incidence trend could be explained by the trend in incidental cases.

To see if this would hold true for the national trend in PCa, conditional probabilities of being incidental from Lothian were applied to all registered cases divided into groups by the same SMR criteria. The extrapolation of conditional probability was based on the assumption of its being the same for other Scottish regions as for Lothian. Therefore, the accuracy of estimated trends of incidental PCa will depend on the validity of this assumption. Variation in practices and policies that can affect the likelihood of a case being incidental, by affecting its SMR criteria used before, may exist between regions, but is unlikely to be sizeable. Besides, the use of 95% confidence limits of the probability to obtain lower and upper limits of estimated number of incidental cases should have contained some of its effect.

Given that, the results in chapter IX show a 5.4% increase in the estimated number of incidental cases in Scotland during 1982-1990. This makes their contribution to the total increase of registered PCa substantial at 34 per cent. This is consistent with the sharp increase in TURP operations performed for BPH patients in Scotland during the same period (chapter VI). But it is lower than that expected if the 14% incidental PCa among BPH patients treated with TURP was applied (Alexander and Boyle 1995).

Analysis of incidence trend components revealed also that 35 per cent of the total increase in registered cases could be explained by ageing. Prostate cancer is a disease of elderly and with the increase in life expectancy more men at risk of developing the disease will accumulate and some will be diagnosed incidentally, after developing symptoms of the disease or even after death on autopsy. The expectation is that this

effect of ageing will become more obvious when the generation of the post second world war "baby boom" reaches the age at which the risk starts to increase (Alexander and Boyle 1995).

Observed trends in cancer incidence data are expected to reflect, partially, improvement in completeness of reporting which is greater in the newer registries (Esteve et al 1994). During the study period prostate cancer incidence in Scotland increased by an estimated 4.2 percent due to improved reporting and the interaction of this component with that of ageing, which equals to 24 percent (131 cases) of the total increase (Table 9.5). An improving trend in completeness could also be indicated from the trend in incidence/mortality ratio (chapter VI).

The small part of the trend remaining could be explained by any other factors that were not taken into account in the previous analysis. This may include any artefact due to increased detection through either screening or increasing autopsy with a policy of including cases detected in this way, or improvement in data quality and also a true increase due to an increase in exposure to risk factors or susceptibility of the population.

A wide-scale screening of apparently healthy individuals normally leads to detection of cases from the pool of hidden undiagnosed disease causing an elevation in the trend which is usually gradual (Muir et al 1994). In Scotland, as well as in other parts of the United Kingdom, however, large-scale screening for PCa is still facing many obstacles (Boyle 1997). There might be some sporadic small screening activities that are unknown, but, if they exist, their contribution is expected to be insignificant.

There is not sufficient information to know the influence of autopsy on the trend of PCa incidence in Scotland, however, if cases detected in this way were reported to the registry they would have been designated as "DCO" cases. On this basis, the influence of autopsy in the trend is unlikely as the percentage of PCa registrations with the DCO designation was declining during the eighties (Black et al 1993). Nonetheless, the matter requires further investigation.

If the percentage of registered PCa cases that are histologically verified is taken as an indicator of data quality, it shows that the SCR data on PCa has improved with time (chapter VI) and thus has affected its morbidity and mortality trends. It is plausible to think of an improvement in patients' acceptance to prostatic biopsy and in the skill of the physician and his intention to do more biopsies on more patients; however, the increased numbers of samples submitted to pathologists could have come mainly from the increasing TURP operation done on BPH patients. If this is the case, some of the effect of improving data quality on the trend would have been accounted for under the effect of TURP discussed earlier. Obviously, the trend in % of histologically-verified cases for clinically-apparent PCa separately will help to clarify this.

The slight increase in age-adjusted incidence rates of clinically-apparent PCa and the slight rise in the mortality rate of the disease very likely indicate that a small part of the overall trend is a true component due to a real increase in the underlying burden of disease.

It might be more useful to discuss whether exposure to any known risk factors is rising. Age is an important determinant of prostate cancer and ageing of the population is a continuing process not only in developed but also in developing

countries as part of the epidemiologic transition (Alexander and Boyle 1995). This, however, will not affect age-adjusted trends.

Results of etiologic studies show quite consistent positive relations between prostate cancer risk and high-fat diet (Kolonel 1996). In Scotland between 1972 and 1990 there was, however, a tendency towards lower consumption of saturated fat and higher consumption of the polyunsaturated fat, as shown by the positive trend in the ratio of the two types (The Scottish Office 1993). This is somewhat incompatible with the theory of dietary fat since higher risk of PCa is associated with the saturated and not the unsaturated fatty acid (Whittemore et al 1995). Reviewing the birth cohort effect for PCa in Japan, Boyle (1993) found the declining trend in prostate cancer mortality among the Japanese born after the Second World War difficult to fit with the same theory since, according to him, those cohorts are more widely exposed to the westernisation of diet in Japan. However, these findings must be taken with care. Correlational studies are usually affected by the ecological fallacy of studying a causal association based on grouped data and confounding (Esteve et al 1994), and concerns should be expressed about the accuracy of dietary intake measurement and its variability with time. The methodology of age-period-cohort modelling is controversial and can give spurious certainty to its results.

Fruits and vegetables, seem to be related to prostate cancer but the findings so far are equivocal. Findings on other food constituents and other life-style factors, such as physical exercise and smoking were inconclusive.

The dietary and life-style hypotheses can not explain the whole ethnic differences in prostate cancer risk, and in the absence of convincing evidence on other environmental factors these differences may suggest an inherited genetic component.

The ethnic distribution of the risk of PCa in Scotland is not known but it is known that incidence rates of prostate cancer is the highest for the blacks in USA. More interesting is that the incidence rates of PCa among Chinese and Japanese immigrants is still lower than that of white Americans while their rates for colorectal cancer (another high-fat diet related cancer) are of the same order (Parkin et al 1992). This has led to the suggestion that either that Chinese and Japanese are less susceptible to prostate cancer than blacks and whites or that the latter groups are exposed to some unknown extraneous factors to which the former groups are not exposed (Zaridze and Boyle 1987). Evidence of the possible inheritance of prostate cancer has been presented (Carter et al 1993) and some progress has been made towards the identification of a susceptibility gene (Smith et al 1996; Cooney et al 1997) but it will be some time before the genetic involvement in the disease development can be established.

In conclusion, a major part of the trend in prostate cancer incidence is artefactual accounted for by improvement in reporting efficiency and increased detection of incidental carcinomas from TURP specimens removed for BPH. Ageing was an important factor in the trend and will continue to be so for the future. However, a component of real increase in the risk of PCa is likely. Future trends of PCa are likely to continue the rise, with screening becoming widespread in many countries, as is now happening in the USA (Potosky et al 1995), with the "baby-boom" taking effect early next century, and with ageing and epidemiologic transition is continuing in many more developing countries (Alexander and Boyle 1995). All that will happen in the absence of any effective preventive measures.

XI. CONCLUSIONS AND RECOMMENDATIONS

1. The increase in prostate cancer incidence in Scotland in the eighties was mostly artefactual. This should not however undermine the relative importance of the disease in public health terms. Epidemiologists though need to take this artefact into account when comparing the Scottish trend with trends in other areas; however, similar artefacts have been observed in other countries.

2. There appears to be a genuine component in the trend. Clinically apparent cases were the majority of reported cases. Their incidence rate and mortality rate have slightly increased. This will be challenging to epidemiologists to investigate the possible increase in exposure to risk factors or determinants of susceptibility. However, their work is not going to be easy because of the obscurity of the disease's aetiology. The genuine component is also an impetus to health planners to make and evaluate plans for its prevention and control including the early detection programmes.

3. Among the artefacts, reporting of PCa was found to be improving with time making an important contribution to the trend of the reported disease incidence. In this respect the capture-recapture method has been a useful tool for assessing completeness of reporting. However, its results should be interpreted with care and attention to the possible bias of dependence of the sources compared.

4. With this method, we estimate that up to 90 per cent of the cases of PCa were registered at the Scottish Cancer Registry. While the possibility of under estimation can not be ruled out the performance of SCR is good but further improvements should be attainable.

5. Increased detection of incidental cancers following TURP operations contributed a substantial proportion to the overall trend. There is no doubt that this is largely an artefact since most of these incidental cancers would have remained latent without progression or endangering the patient's life. Identification of these cases is therefore important for the quantification of this artefact and for interpretation of the trend.

6. Review of hospital case notes is the most reliable method of identifying incidental cases. However, for examining their past trend this method is hampered by missing or incomplete notes, the difficulty in interpreting physician's writing and its cost. The alternative presented in this thesis was to use limited hospital data routinely available on the SMR system and a sample case-note review. This permitted assessing the predictability of routine data against the review findings. This method was cheap, and feasible and some of its criteria had high predictibility for a case to be incidental (90%). Validation of these predictibility estimates on an independent data set is recommended.

7. Ageing has undoubtedly been an important component in the trends of the disease and is likely to exacerbate in the future. So, health care and finance managers should prepare themselves for the increasing workload and ensure accessible and efficient services.

8. Finally, the SCR (SMR6) and the hospital morbidity (SMR1) data systems and the linkage between them was a crucially useful research tool in this project. Researchers should be encouraged to use these systems, but must remember that quality control checks will be their responsibility as well as that of ISD.

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APPENDIX A
DATA SET VALIDATION (CHAPTER VII)

1. Total number of PCa registered cases

To assess reliability of the original data supplied by the ISD, the number of prostate cancer cases with SMR6 record in the data set was compared with the number of cases published in the latest ISD cancer statistics report (Sharp et al, 1993). The data initially supplied had 756 cases less than the published data, which is just above 7%, spread over the ten year period from 1982 to 1990 (Figure A.1). Investigation for possible causes, at ISD, revealed some errors in the data abstraction programme the correction of which, has led to recovery of 476 cases leaving a deficiency of 280 cases (2.7%).

Thus the final data for analyses reported here have this small shortage in the number of cases which is unavoidable, and could be attributed to the difference in preparation of published and the study data sets, especially in matching score level chosen for record linkage. In the ISD, linkage between pairs of records that belong to the same individual is based on a probability matching method, as opposed to exact matching method (Gill and Baldwin, 1987),which always carries the risk of mismatching i.e. matching records that do not in fact belong to the same individual and vice versa. Kendrick and Clarke (1993) have estimated this error in the ISD linkage system at around 1% (including both false positive and false negative rates) but it could vary according to the point of matching score chosen to distinguish matched and un-matched records. The higher the score point the greater the chance that we miss correct matches, and the lower this threshold is the more we are likely to accept false positive matches (Gill and Baldwin, 1987).

According to this it is possible that a lower matching score threshold was chosen for the study data than the one used in published data, in which case it is very likely that published data have some duplicates. On the other hand, we may have matched some records, in the data set, that do not belong to the same individual (false positive matches). However, this error is self-adjusting (false-positive versus false negative) which should have very slight effect, if there was any, on interpretation of the disease trend.

Another potential source of matching error in our data set was the linkage of SMR1 for prostate cancer with SMR6 due to duplicate recording in SMR1 where each admission for prostate cancer generates a new record for the patient. At ISD level, this was dealt with, in our study, by selecting the first record with PCa diagnosis from all patient's records ordered by the date of admission. To ensure further that the selected SMR1 record is the one related to PCa diagnosis, cases were classified into consistent and inconsistent matches depending on whether or not the two (SMR1 and SMR6) matched records fall within ± one year time interval between admission date and date treatment commenced (the anniversary date).

2. Relative completeness of PCa registration

A preliminary analysis was conducted to determine the level of completeness of SCR for PCa cases who have had an SMR1 for PCa during the study period (1982-1990). Capture-recapture method has also been applied as it is described in this chapter main methods section to assess SCR completeness taking into account some cases that could have been missed by SMR1.

The results from these two analyses are shown in figure A.2. They revealed that completeness of SCR was generally below expectation; the highest estimated level was 88.3% in the year 1990. It was particularly markedly lower in the first three years of the study compared to following years.

These findings were below expectation because they were incomparable with an old estimate of cancer registration completeness depicted for the seventies by an advisory committee on cancer services in Scotland (Planning council, 1979). Given a presumed great similarity in many of cancer registration-related aspects, particularly physicians' and staff attitude and performance, between Scotland and other parts of the UK, these results are not comparable with an 80.7% completeness of PCa registration reported for the North-Western region of England in 1974-75 (Benn et al 1982), which is even slightly better than the 1984 estimated completeness in Scotland that was 80.5%.

Trying to find an explanation to this striking low completeness it was suggested, by ISD staff, that some of the cases with SMR1 records in the first few years of linkage beginning from 1981 could have matched SMR6 registration record before 1981 and thus have not been encountered in linkage. This has been confirmed and has necessitated a repeat analysis after allowing for those early SMR6 records if they match an SMR1 record in the study period.

Figure A.1 Annual and total number of prostate cancer cases in published reports and the study data sets in Scotland

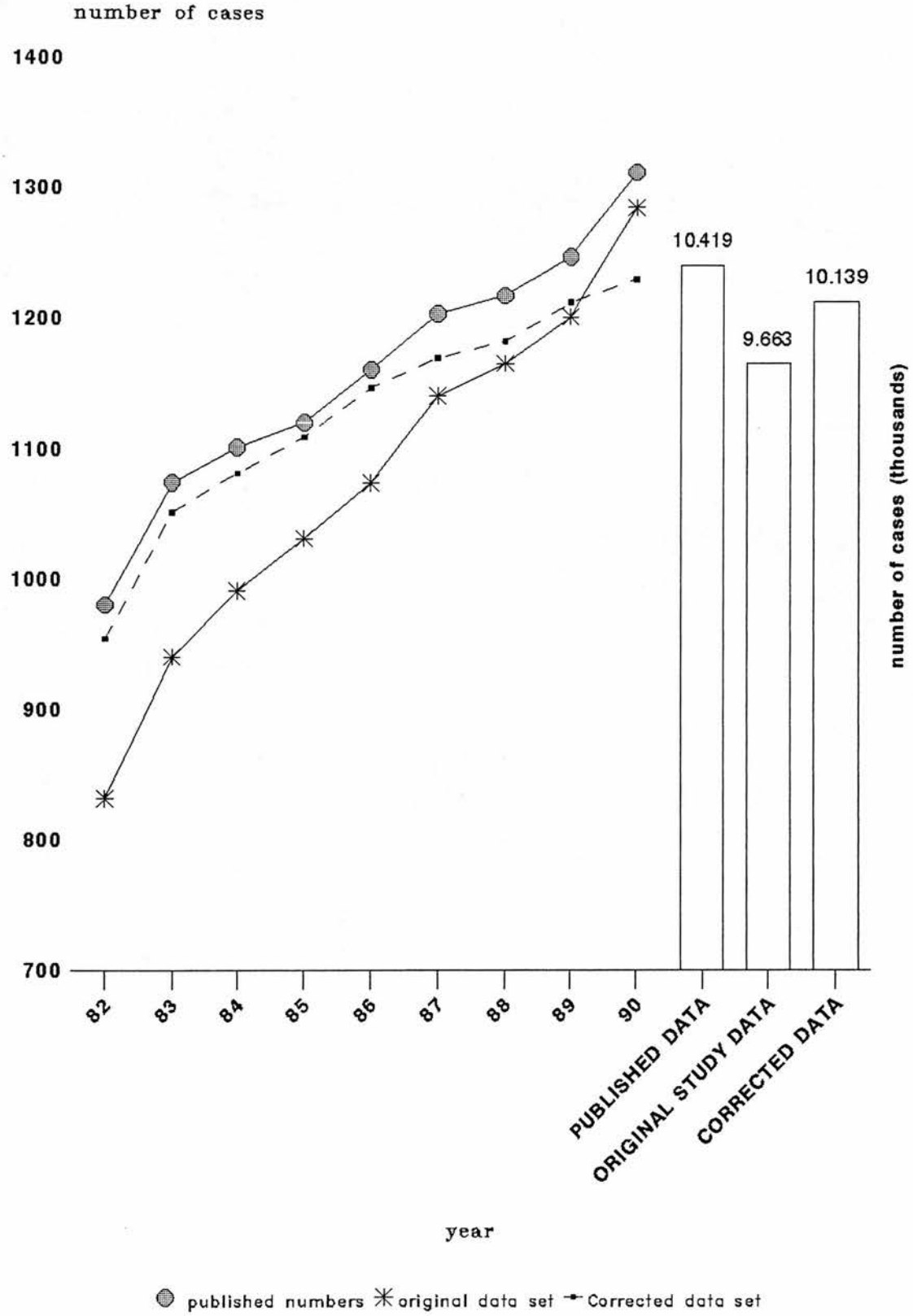
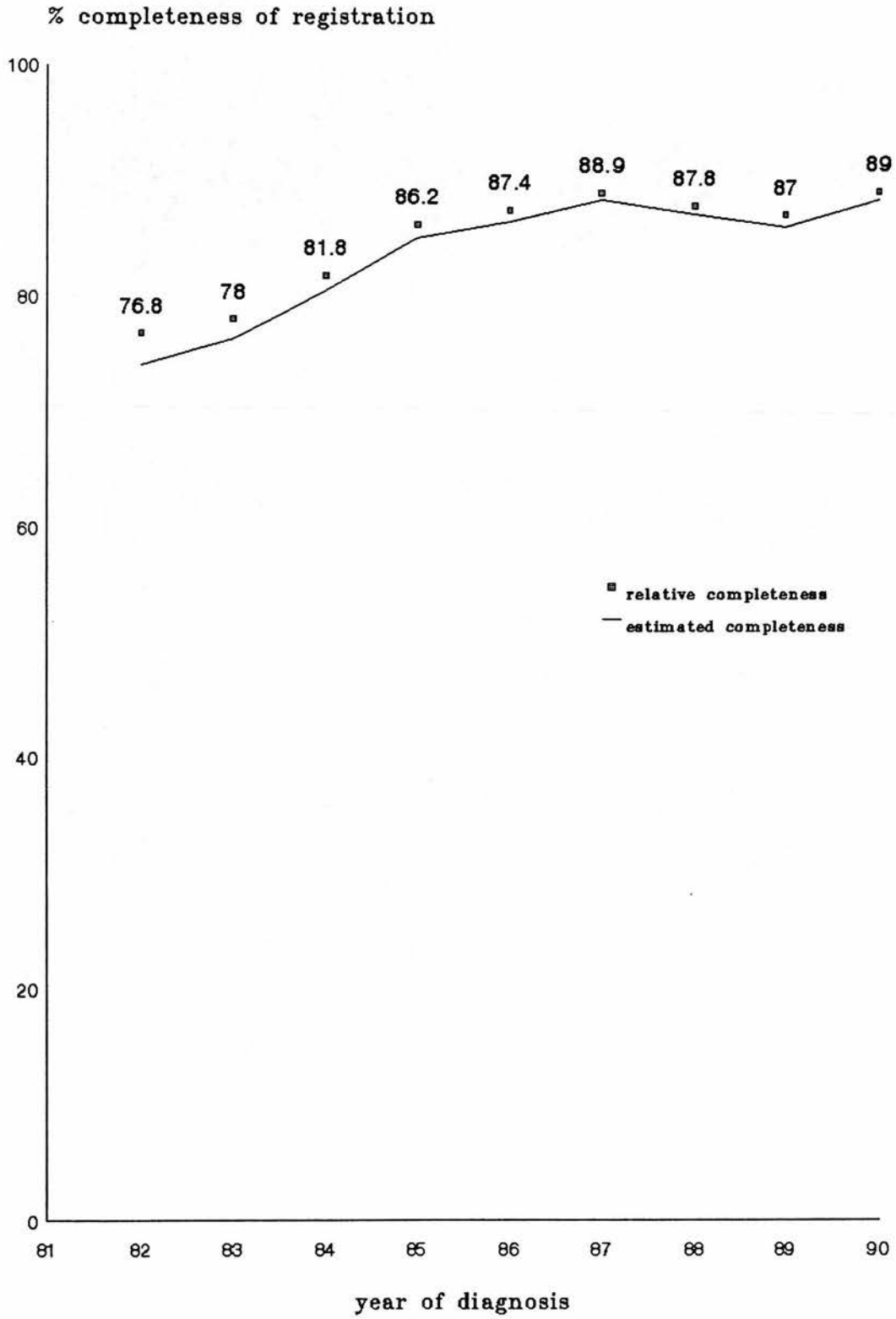


Figure A.2 Relative and estimated completeness of registration of prostate cancer in Scotland (provisional analysis)



APPENDIX B

STUDY OF TURP-ASSOCIATED DIAGNOSIS OF PROSTATE CANCER IN LOTHIAN 1982-1990

I. PERSONAL DATA:

1. Sample reference No:

2. Surname:

3. Forename(s):

4. Patient's Date of Birth (day/month/year):

5. Unit No:

6. Hospital code:

II. Prostatic surgery record up to definitive diagnosis of PCa

Sample reference No:

Date	Type of surgery	Reason for surgery	Surgeon's DX after surgery	Histology done	Histological findings and DX	Stage T N M		

III. Other examinations of prostate up to PCa diagnosis (DRE, PSA, TRUS, CATS, Bone Scan)

Sample reference No:

Date	Examination	Reason for examination	Findings	Further management	Stage if PCa		
					T	N	M

APPENDIX C

STUDY OF TURP-ASSOCIATED DIAGNOSES OF PCa
CLINICAL DATA CODING FORM

SRNum [ ]

Were notes available? Notesav 1=Yes complete 2=Yes adequate but incomplete

3=Yes inadequate 4=No [ ]

Has the case been diagnosed as PCa?

PCadiag 1=Yes primary 2=No 3=No secondary [ ]

DRE:

Number of urologist examinations: DREnum [ ]

Results of each (1=malignancy mentioned, 2=+ve signs without -ve signs, 3=mixed signs, 4=-ve signs, 5=benign stated)

DRE1date [ ] DRE1find [ ]

DRE2date [ ] DRE2find [ ]

DRE3date [ ] DRE3find [ ]

DRE4date [ ] DRE4find [ ]

Was DRE done under GA? DREGAdon 1=Yes 2=No [ ] If yes ,

DREGAdate [ ] DREGAfind [ ]

TURP:

Number of TURP operations: TURPnum [ ]

If >0 TURPs was malignancy found at any one? TURfound 1=Yes 2=No [ ]

If yes,

TURPdate [ ]

Pathological extent of PCa: PATHext 1= ≤ 3 foci or chips OR ≤ 5% of tissue

2 = not certain or > code 1 [ ]

BIOPSY:

Was biopsy done? BIOPdone 1=Yes, 2=No [ ] If yes,

BIOPdate [ ] BIOPfind 1=PCa , 2=Not PCa [ ] BIOPtype 1=tru-cut 2=FNA 3=other prostatectomies [ ]

METASTASES:

Were any bone scan done before or after diagnosis? BSdone 1=Yes, 2=No [ ]

If yes,

BS1date [ ] BS1find 1= metastases found 2=No metastases [ ]

BS2date [ ] BS2find 1= metastases found 2=No metastases [ ]

Was there any other mention of distant metastases?

Meta 1=Yes 2=No mention [ ]

If yes, Metadate [ ]

Was M-stage specified in the notes after diagnosis? Mstagesp 1=Yes 2=No [ ]

If yes, when and what was it?

MSdate1 [ ] Mstage1 [ ]

Mdate2 [ ] Mstage2 [ ]

AUTOPSY:

Was autopsy done? AUTOdone 1=Yes, 2=No or no mention [ ] If yes,

AUTOdate [ ] AUTOfind 1=PCa, 2=No PCa [ ]

T-STAGE:

Is there any statement of T-stage in the case notes ?

TSmentio 1=Yes, 2=No [ ] If yes, how many times TStimes [ ]

What are these stages:

TS1date [ ] TS1 [ ]

TS2date [ ] TS2 [ ]

TS3date [ ] TS3 [ ]

Is presence of local extension mentioned in the notes?

LOEXpres 1=Yes, 2=No [ ]

If yes, what was the first date? LOEXdate [ ]

[Note that this form is for input to EPIINFO and encodes variable names]

APPENDIX D

1. DRE Suspicion : Individual Examiners

Code	Meaning	Criteria
8	No DRE	DRE was not done at all
1	Definitely suspicious	EITHER (i) Malignancy mentioned as diagnosis OR (ii) Described as 'very hard' and/or 'fixed' and/or 'grossly asymmetrical' and biopsy done after the DRE
2	Probably suspicious	Not code 1 BUT (i) Suspicious signs noted (i.e. very hard and/or fixation and/or gross asymmetry) AND (ii) No benign signs noted (i.e. smooth, soft, symmetrical)
3	Equivocal	None of the other categories
4	Probably not suspicious	Benign signs noted (i.e. 'smooth' and/or 'soft' and/or 'symmetrical') although suspicious signs could be also mentioned (but not 5 below)
5	Definitely not suspicious	EITHER BPH mentioned specifically as diagnosis OR malignancy denied (e.g. the gland is craggy but does not look malignant) OR benign signs noted and no malignant ones mentioned

2. Overall DRE Suspicion (Combination of examiners)[1]

Code	Meaning	Criteria
8	Not applicable	No relevant DRE i.e. DRE was not done or DRE was done >1 year before or >2 months after diagnosis
1	Definitely suspicious	Code 1 for each individual DRE OR GA DRE =1 and other DREs ≤ 2
2	Probably suspicious	Overall code ≠ 1 but: Code 1/2 for EITHER each DRE OR GA DRE
3	Equivocal	None of 1,2,4,5
4	Probably not suspicious	Not overall code 5 but Code 4/5 for EITHER each DRE OR GA DRE
5	Definitely not suspicious	EITHER Code 5 for each individual DRE OR GA DRE =5 and other DREs ≥ 4 or no other DREs in 2 months to diagnosis

[1] Refers only to DRE done by a urologist - others are ignored. Also, (a): if there is at least one DRE within 2 months of diagnosis, overall DRE is calculated only from DREs done in this time, (b): otherwise it is calculated from the most recent DRE up to 1 year before diagnosis - in which case codes of 5 are downgraded to 4.

3. Appropriateness of DRE Suspicion

Code	Meaning	Criteria[1]
8	Not applicable	Overall DRE not equal 1,2 OR 3
1	Definitely not appropriate	EITHER Case not PCa OR Pathology revealed tumour of ≤3 foci, ≤3 chips or in ≤ 5% of tissue resected
2	Probably not appropriate	Not appropriateness code 1,8 But biopsy done after last DRE prior to or at the same time of TURP was negative
3	Unsure	Not code 1,2,4,5,8
4	Probably appropriate	Overall DRE=2 and not appropriate-ness code 1,2,5
5	Definitely appropriate	Not appropriateness code 1,2 and overall DRE code is not 3 and: EITHER biopsy done prior to or at the same time of TURP was positive OR Overall DRE = 1 and not appropriateness code 1

[1] Biopsy refers to lesion biopsy conducted in response to DRE

4. Classification of Incidental carcinomas
(Essentially stages T1a & T1b excluding M_1)

Code	Meaning	Criteria
1	Definitely TURP-detected incidental ("TURINC")	(i) Overall DRE code 5 AND (ii) PCa detected at TURP AND (iii) Bone scan done up to 2 month after diagnosis was negative AND (iv) No mention in notes of distant metastases or positive M-stage or local extension up to 2 months after diagnosis AND (v) No mention in notes of stage T2+ up to point of diagnosis AND (vi) No mention in notes of stage T3+ up to 2 months of after diagnosis
2	Probably TURP-detected incidental	Not any of code 1,4 or 5 AND (i) Overall DRE code 4/5 OR (overall DRE code = 1,2,3 and Inappropriate) OR (overall DRE code = 8 and pathological extent of the tumour is T1a). AND (ii) PCa found at TURP AND (iii) No mention in notes of distant metastases, local extension or T3+ up to 2 months after diagnosis AND (iv) No mention in notes of stage T2+ up to point of diagnosis
3	Unclassifiable	None of 1,2,4,5

(Cont'd....)

(.....Cont'd)

Code	Meaning	Criteria
4	Probably not TURP-detected incidental	Not 5 but EITHER (i) Overall DRE code was 3-5 AND a DRE done up to 2 months after diagnosis was of code 1 or 2 OR (ii) overall DRE code was 2 and not inappropriate OR (iii) local extension was mentioned in notes up to 2 months after diagnosis OR (iv) T2+ stage was mentioned in notes before diagnosis OR (v) T3+ stage was mentioned in notes up to 2 months after diagnosis
5	Definitely not TURP-detected incidental	EITHER (i) TURP was not done (prior to diagnosis) or no histology of the chips or negative histology OR (ii) Evidence of M_1 status or positive bone scan up to 2 months after TURP OR (iii) Biopsy done prior to or at the same time of TURP was positive OR (iv) overall DRE code was 1 and not inappropriate

APPENDIX E

1. ESTIMATION OF THE NUMBER OF "TURINC" PCa IN THE SAMPLE

1.1 Derivation of estimated total number of "TURINC" cases

1.1.1 minimum estimated number is equal to the number of TURINC cases observed (classified) from the valid case notes.

1.1.2 maximum estimated number is equal to the sum of observed TURINC cases and all missing cases including those with non-valid notes.

1.1.3 average estimated number is equal to the number of "TURINC" cases observed from valid case notes plus estimates of their count among missing cases grouped into SMR incidental "SMRINC" groups. The second component was derived as follows:

(a) Formation of "SMRINC" probability groups: The criteria used for the sample groups (see methods) were intended to choose, very broadly, cases that were possibly TURP-detected incidental "TURINC" cases. These criteria and others related were tested for their capability to discriminate between true "TURINC" and other cases classified by the case note review. This showed that with slight modification in these sampling criteria a significant discrimination was attained (Alexander F: Personal communication). According to this, valid cases with incidental status available (n=142) were categorised by two criteria into four "SMRINC" groups as shown in table E.1, along with the proportions of truly "TURINC" cases in each group (P_k). For simplicity the groups will be called "higher, middle, middle-low and low incidental probability groups". Table E.2 shows the distribution of cases in these "SMRINC" groups and the sampling groups.

(b) Calculation of the estimate:

(i) missing cases, excluding those who had died of PCa (who were taken to be NOT TURINC), were grouped by age and the same "SMRINC" groups (Table E.3).

(ii) Assuming that valid and missing cases in these "SMRINC" groups have equal chances of being "TURINC", the number of these among missing cases was estimated for each age group separately, and summed according to the following formula:

number of "TURINC" cases = Σ_{ik} (M_{ik} x P_k) .....(1) where,

M_{ik} = number of missing cases in ith age group and kth "SMRINC" group,
P_k = proportion of "TURINC" cases in the corresponding "SMRINC" group of valid cases.

Table E.1 distribution of valid selected cases of PCa in Lothian among SMRINC probability groups

"SMRINC" probability groups	presence of BPH on SMR1 for PCa	TURP-diagnosis duration	No. incidental / total P_k
1 High	1	1	40/44 **(P_1)**
2 Middle	1	0	5/11 **(P_2)**
3 Middle-low	2	1	22/47 **(P_3)**
4 Low	2	0	12/40 **(P_4)**

Explanation of the table codes:

Criteria 1: Presence of BPH diagnosis on SMR1 for PCa
1= BPH is present on SMR1 for PCa or there is no SMR1 for PCa
2= BPH is not present on SMR1 for PCa which exists

Criteria 2: TURP-diagnosis date duration
1= TURP date <= PCa date <= TURP date + 3 months
0= Others including absence of SMR1 for TURP
Note that PCa date is taken from SMR6 if no SMR1 is present for PCa

Table E.2 Distribution of valid selected cases of PCa in the sampling and "SMRINC" groups

SMRINC probability group	sampling groups				total No of cases
	1a	1b	1c	2	
1 High	32	10	2		44
2 Middle		2	6	3	11
3 Middle-low	19		19	9	47
4 Low	4		29	7	40
total	55	12	56	19	142

Table E.3 Distribution of missing cases in "SMRINC" groups by age

patient's age	"SMRINC" probability groups			
	1	2	3	4
55-64 years	0 ($\mathbf{M_{ik}}$)	1	0	0
65-79 years	5	2	4	6

1.2 Derivation of estimate number of "TURINC" cases by period of registration

1.2.1 Average estimate

Average period-specific estimate is equal to the sum of number of "TURINC" cases observed from valid case notes in a specific period plus their count among missing cases in the same period. The second component was obtained as follows:

(a) missing cases in a specific period, excluding those who had died of the disease, were tabulated by age and "SMRINC" probability groups.

(b) applying formula (1), number of "TURINC" among missing cases in a specific period is equal to the sum of, number of missing cases in each age-"SMRINC" group x p_k (observed probability of "TURINC" in SMRINC group).

2. DETERMINATION OF NUMBER OF "TURINC" CASES IN THE STUDY POPULATION

2.1 Estimated total number:

total number (minimum, maximum, average) =
number of "TURINC" cases estimated in the sample + number of "TURINC" in the unselected batch of group 2.

2.1.1 The first component is obtained under section 1 above.

2.1.2 The second is obtained as follows:

(a) calculation of probabilities of "TURINC" cases in the selected batch of group 2:

(i) the number of "TURINC" cases in the selected batch were estimated above in the sample.

(ii) Minimum, maximum and average probabilities were then calculated by dividing the estimated (minimum, maximum, average) number of "TURINC" cases by the total number of cases in the batch (N=25).

(b) probabilities calculated in (ii) above are applied to the number of unselected cases in group 2 to obtain estimated numbers of "TURINC":

minimum number = 30 x minimum probability

maximum number = 30 x maximum probability

average number = 30 x average probability

2.1.3 The numbers derived under (b) are summed with the first component (the corresponding numbers of these cases estimated in the sample) to obtain the three estimates of the total number of "TURINC" cases in the study population in Lothian.

Table E.4 Distribution of cases in the selected group 2 batch by period of registration and incidental nature

Period of registration	TURINC status			
	TURINC	NOT TURINC	uncertain	missing cases
82-84	2	6	1	4*
88-90	5	6		1

* one case died of prostate cancer and thus was classified as not incidental.

Table E.5 Distribution of missing cases in selected group 2 by age and SMRINC probability groups

patient's age	SMRINC probability groups			
	1	2	3	4
55-64 years	0	1	0	0
65-79 years	0	0	2	2

2.2 number of "TURINC" cases by period of registration

number (minimum, maximum, average) of "TURINC" cases in each period = number estimated in the sample in that period + their count estimated in the unselected batch of group 2 of sampling in the same period.

2.2.1 The first component is obtained as under section 1.2 above.

2.2.2 The second is obtained as follows:

(a) period-specific numbers and probabilities of incidentals in the selected cases of group 2 were estimated as above (2.1.2.a).

(b) calculated period-specific probabilities of TURINC were used in place of overall ones.