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Increasing detection of significant prostate cancer in younger men – ten year trends in prostate cancer risk profile in the Mid-West of Ireland

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Introduction Although PSA (prostate specific antigen) based screening for prostate cancer (PCa) is controversial, an increasing number of men are undergoing Transrectal Ultrasound Guided prostate biopsy (TRUSPB) through primary care-based PSA testing and referral to hospitals. The aim of our study was to investigate presenting risk profiles of PCa over the last decade in a cohort of men in Ireland and to examine any change in the same over this time period.
Material and methods The hospital patient administration system was analysed for patients who underwent TRUSPB from January 2005 to December 2015. Clinically significant PCa was defined as Gleason score of 7 or above.
Results Complete data was available on 2391 TRUSPB patients: number of biopsies increased by 53%, median age decreased by 0.9%, median PSA decreased by 6% (p = 0.001, ANOVA) and abnormal DRE increased by 9% (p = 0.001, chi square). Overall positive biopsy was 44% and significant cancer rate was 21%. There was a significant change in trend of detection (p = 0.02) with average annual increase in significant cancer of 3%. The median age of the significant cancer cohort reduced by 1% and the PSA at diagnosis reduced by 9%. In younger men (<50 years), the rate of significant cancer detection increased by 18%.
Conclusions Significant PCa detection increased across all age groups but recently, a younger patient profile was diagnosed with high-grade disease. This paves the way for future research on early-onset PCa. Younger patients with significant disease would result in increasing number of patients being eligible for radical treatment with implications on health resource planning and provision.

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INTRODUCTION

PSA (prostate specific antigen) based screening for prostate cancer (PCa) is controversial, but increasing. An increasing number of men are undergoing Transrectal Ultrasound Guided prostate biopsy (TRUSPB) through primary care-based prostate specific antigen (PSA) testing and referral to hospitals. The incidence of prostate cancer is heavily influenced by the widespread use of PSA testing. The 2016 EAU guidelines suggest adopting a special-

ised risk-adapted strategy for early detection of prostate cancer (Pca) in well-informed men with good performance status and life expectancy of 10–15 years. The guidelines recommend offering PSA screening in men with an elevated risk of PCa along with appropriate counseling on risks and benefits [1]. Currently, patients who have a high PSA or/and abnormal Digital Rectal Examination (DRE) are advised to undergo prostate biopsy. As of now, transrectal ultrasound guided prostate biopsy (TRUS-PB) is the most commonly used modality for tissue

diagnosis of PCa. This method was introduced in the mid 1980s and since then it has also seen significant changes in its execution [2]. Current recommendations are a 10–12 core TRUSPB in indicated patients. According to the National Cancer Registry Ireland [3], there were 3,400 cases of PCa diagnosed between 2011 and 2013, making up one-third of all male cancers detected in this period. Of the 28,432 patients diagnosed with PCa since 1994, 37% died by the end of 2013. PCa incidence is among the highest in Europe and incidence rates in Ireland are up to 1.5 times higher than in the United Kingdom (UK) and Europe as of 2012 [4]. The etiology of PCa is still not clearly understood; genetic predisposition and environmental factors both seem to contribute. Age, ethnic background and family history are the most prominent risk factors. In recent years, interest has arisen in the changing presenting risk profile of prostate cancer. The overall rate of new PCa diagnosis in the United States is dropping by an average of 5.1% per year while death rates have also been decreasing by 3.5% each year between 2004–2013 [5]. Contrary to this, the age-standardised incidence of PCa in Ireland has been steadily rising at a rate of 1% per year in the last decade [4]. PCa incidence in the UK has increased by 155% since the 1970s and the age-standardised incidence in Europe has more than doubled [6].

There is limited published data on the changing disease risk profile at diagnosis. The aim of our study was to investigate presenting risk profiles of PCa over the last decade in a cohort of men in Ireland and to examine any change in the same over this time period.

MATERIAL AND METHODS

This was retrospective cohort study on patients who underwent TRUSPB in our hospital between January 2005 and December 2015. Ethical approval was obtained from the local ethics committee. The hospital patient administration system was utilised for collection of data.

Patients with unknown histopathology result and patients who underwent trans-perineal biopsy of prostate were excluded. All biopsies were performed by four consultants over the ten-year period. TRUS biopsies were performed using a standard ultrasound and biopsy probe with prophylactic antimicrobial cover as per the current guidelines (oral Ciprofloxacin 500 mg the morning and evening of biopsy and Gentamicin 240 mg IV at the time of biopsy).

Details were obtained on patient demographics, digital rectal examination (DRE) findings, PSA, biopsy cores and histology report. Clinically significant Pca was defined as Gleason score of 7 or above. Primary

outcome measures were trends in patient risk profile, cancer detection rates and Gleason grade. Our secondary outcome measures included demographic trends in the significant cancer sub-group and cancer detection rates in younger men (<50 years).

All data was analysed with SPSS version 24.0 and excel. Trends were expressed as average annual percent changes over the decade. P value of less than 0.05 was considered statistically significant. ANOVA, Student's t test and Chi-square tests were used where appropriate.

RESULTS

A total of 2391 TRUSPB biopsies were performed over the ten-year period. There was a 53% rise in TRUSPB performed in the center over the decade. Age (Figure 1): The median age of the cohort was 63 years. The median age of the patients undergoing TRUS biopsies decreased over the ten-year period by 0.9% from 65 years to 63 years (p = 0.001, ANOVA). PSA (Figure 2): The median PSA of the cohort was
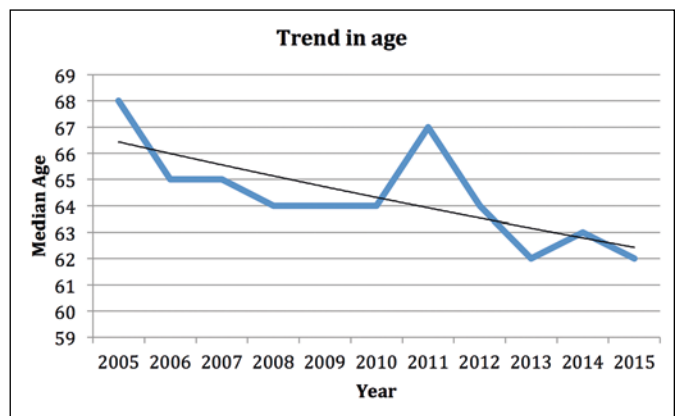

Figure 1. *Trends in age of men undergoing Transrectal Ultrasound Guided prostate biopsy over the last decade.*
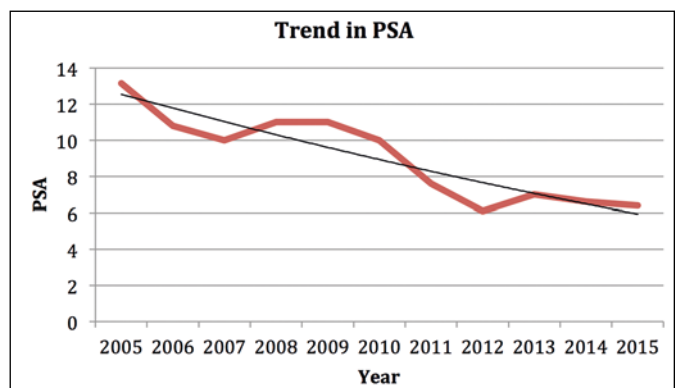

Figure 2. *Trends in prostate specific antigen (PSA) at diagnosis in men undergoing prostate biopsy over the last decade.*

8.2. The median pre-biopsy PSA reduced by 6% over the decade (p = 0.001, ANOVA) from 10 (2005–2010) to 6.9 (2011–2015).

Biopsy cores: The median number of cores per biopsy increased over time as expected by 15% per year from 4 (2005–2007), 8 (2008–2010) to 12 (2011–2015) (p = 0.001, ANOVA).

DRE (Figure 3): Overall 35% of patients undergoing TRUS biopsy had a suspicious/abnormal DRE. Proportion of abnormal DRE increased over the decade by 9% (p = 0.001, chi square).

Cancer detection (Figure 4)

Subgroup analysis: significant cancer cohort

We performed a further subgroup analysis of the patients with a diagnosis of significant cancer (n = 494). We found the median age of the significant cancer cohort was 65 years, which reduced by 1% per year over the period. The median age of this cohort in 2015 was 63 years, which was significantly lower than that in 2005 of 71 years. The median PSA was 10.6 ng/ml in this cohort and it steadily declined by 7% per year over ten years, the initial median PSA in 2005 was 27 ng/ml which reduced significantly to 8.3 ng/ml by 2015. The abnormal DRE rate was 41.3%, which also increased by 48% over the ten-year period.

Subgroup analysis: younger men <50 years of age (Figure 5)

We analysed men of age equal to or less than 50 years who underwent TRUSPB in the institute (n = 61) and found a linear increase in the rate of significant cancer detection rate by 18%/year over the last decade. The overall negative biopsy rates in this cohort was 65% (n–39), with a 25% (n = 15) overall significant cancer detection rate.

DISCUSSION

Our study shows that the rate of TRUSPB being performed in this single centre in Ireland rose dramatically over the last decade. This study also showed that an increasing number of younger men are presenting with lower PSA. This is likely a reflection of increased PSA testing.

Screening for PCa is currently the most controversial topic in urological literature. The median age of PCa detection has reduced in the last 30 years, which could be attributed to PSA use. Annual screening with PSA increases lifetime risk of PCa diagnosis from 8% to 20% [1]. A population based study of PSA screening from Australia published
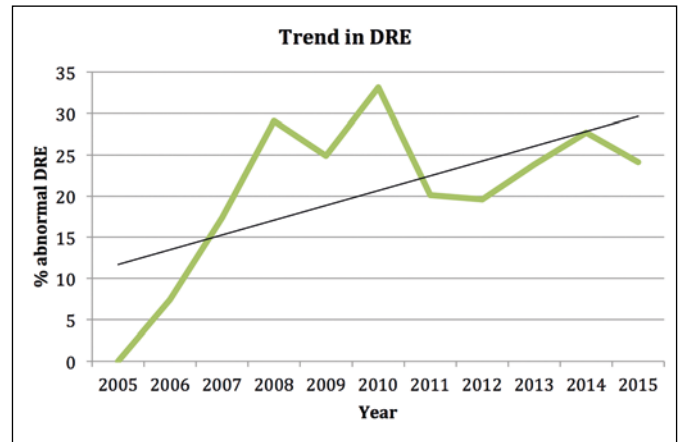

Figure 3. *Trends in abnormal Digital Rectal Examination (DRE) rates prior to prostate biopsy.*
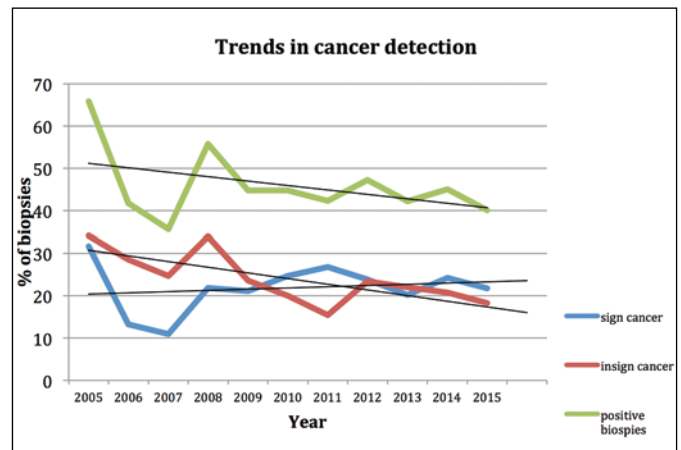

Figure 4. *Trends in cancer detection in men undergoing prostate biopsy in the last decade.*
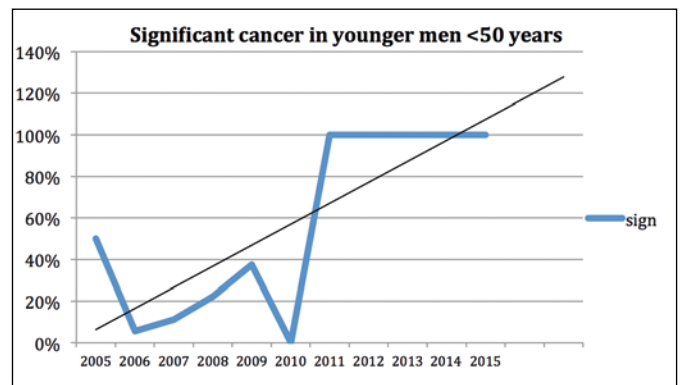

Figure 5. *Trends in significant cancer detection in men <50 years undergoing prostate biopsy over the last decade.*

in 2013, showed increasing incidence of PSA testing in men <55 years of age leading to modestly higher incidence of PCa in Australia [7]. Merits of PSA

screening are controversial and most guidelines recommend no PSA screening in men <40 years of age. The Surveillance, Epidemiology, and End Results (SEER) program has also showed that PSA screening in younger men has led to almost an additional million men being over diagnosed and over treated for PCa, with no overall survival benefits [8]. The US Preventive Services Task Force (USPSTF) recommended against PSA screening in all men in 2012, since then the overall rates of PSA screening in the US have declined as has the incidence of early stage PCa [9]. PSA screening is not offered routinely in Ireland and other European countries. However, the National Cancer Registry in Ireland (NCRI) reports an almost 9% rise in rates of PSA testing in Ireland based on laboratory data from 2008–2010 [10]. This increased rate of opportunistic PSA screening and consequent TRUSPB could be attributed to increasing awareness and concern among the patient population secondary to the media, internet and possible increased screening in other family members due to rising awareness of risk of familial PCa. Interestingly, in this study there was also an increase in the rate of abnormal DRE in patients undergoing TRUSPB, hence opportunistic PSA screening may not be the sole indication for rising rates of TRUSPB in this cohort.

With higher rates of opportunistic PSA screening, there has reportedly been a significant stage shift in PCa from locally, advanced metastatic PCa to early stage, lower volume PCa [11]. The NCRI reports a continued increase in T1 and T1c stages of PCa in the last decade but leveling off of the T2 cancer cases in line with the overall incidence [4]. However, a recent report from the US showed a significant increase in the incidence of metastatic PCa since 2007, the largest increase was seen in men aged 55–69 years [12]. They showed reduction in incidence of low-risk PCa, rise in intermediate and high risk PCa from 2004 to 2008 and a steady state in these trends there after. A 2013 UK study by Greenberg and colleagues [13] found that there was a significant upward migration in intermediate and high-grade histological diagnosis of prostate cancer over the previous decade. Li and colleagues [14] in their study on trends in PCa also showed a significant increase in rate of poorly differentiated PCa (Gleason 7 or more) in their study population from 2004–2007, with a simultaneous decrease in the well-differentiated and moderately differentiated cancer groups. They labeled this partly because of the introduction of higher tertiary Gleason patterns and reporting different Gleason grades in multiple needle biopsies. Even so, we cannot completely rule out the changing natural history of the disease and possible behavioral and environmental exposures leading to more aggressive disease. We looked at PCa detection rates in the patients undergoing TRUSPB in the last decade in this centre and found that although overall positive biopsy rates dropped over time, the significant cancer detection rate increased by 3% per year over the last ten years.

This could in part be attributed to the changing format of TRUSPB in the last decade with increasing number of core biopsies through the study period. The median number of cores taken during the TRUSPB in this center rose from 4 to 12 in the last decade, in line with changing recommendations. The original six-core biopsy introduced by Hodge had a false negative rate of 22–30%. The cancer detection rate seems to increase with increasing number of cores: two consecutive sextant biopsies have a 75% cancer detection rate, two consecutive 10-core biopsies have a 90% cancer detection rate [15]. The current EAU recommendation is to perform a 10–12 core TRUSPB.

We analysed demographic trends in patients with a diagnosis of significant PCa in the last decade and found increasingly younger men with lower PSA were being diagnosed with significant PCa. Further analysis of younger men <50 years of age showed a steady rise in rate of significant cancer detection. There has been a rise in incidence of PCa in younger men in recent times by almost 5.7 fold with the median age at diagnosis shifting from 72 years in 1986 to 67 years in 2009 [16]. In Ireland as well, the age group below 55 years shows the highest relative increase in PCa incidence [4]. Early onset PCa in men below the age of 55 years could be a distinct phenotype from an etiological and clinical perspective, with a possible strong genetic component. Though younger men are more likely to have low-grade disease, among men with high Gleason grade or locally advanced cancer at diagnosis, younger men are reported to have a particularly poor prognosis [16, 17]. Younger men with high-grade disease are at a much higher risk of death from PCa regardless of the type of therapy they undergo [17]. The declining age of the patient population being diagnosed with significant PCa also has serious implications on healthcare resource planning and allocation. These men have a longer life expectancy and hence are candidates for radical treatment. Studies have also showed that men younger than 65 years diagnosed with PCa often opt for curative treatment compared to their older counterparts and also place increased importance on functional outcomes of the treatment such as sexual function and urinary continence, the former being of increased consequence [16].

There are several limitations of this study. This was a retrospective single centre study that reduces generalisability but it also reduces observer variability especially in histological grading of prostate cancer.

CONCLUSIONS

This trends study on patients undergoing TRUSPB in the last decade in a single center revealed an increasing rate of biopsies inline with the incidence trend of PCa in Ireland. Younger men with lower PSA are increasingly undergoing biopsies reflecting the escalation in opportunistic PSA testing. Signifi-cant PCa detection increased across all age groups in the last decade but a younger patient profile was diagnosed with high-grade disease in recent times. This paves the way for future research on early-onset PCa and studies looking at possible genetic or environmental factors contributing to this trend. Younger patients with significant disease would result in increasing number of patients being eligible for radical treatment with implications on health resource planning and provision.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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