EUROPEAN JOURNAL OF CANCER 46 (2010) 3068–3072

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Detection rates of cancer, high grade PIN and atypical lesions suspicious for cancer in the European Randomized Study of Screening for Prostate Cancer

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ARTICLE INFO

Article history:
Received 27 June 2010
Received in revised form 21 September 2010
Accepted 21 September 2010

Keywords:
ASAP
PIN
Prostate cancer
PSA
Screening

ABSTRACT

The aim of the study: This article presents the incidence of prostate cancer, isolated high grade prostatic intraepithelial neoplasia (PIN) and atypical lesions suspicious for prostate cancer (LSPC) during subsequent screening rounds in the centres of five of the countries participating in the European Randomized Study of Screening for Prostate Cancer (ERSPC). The incidence and predictive value of high grade PIN and LSPC for prostate cancer in subsequent biopsy following these diagnoses were evaluated.

Patients and methods: Study group consisted of 56,653 screened men in the ERSPC centres of Finland, Italy, Netherlands, Sweden and Switzerland, who underwent 3–7 screening rounds at 2–4 year interval. Data for prostate cancer were obtained from the ERSPC central database. Data for high grade PIN and LSPC were gathered from each ERSPC centre. Detection rates of subsequent prostate cancer in the first re-biopsy after these diagnoses were determined.

Results: The average cancer detection rate was 3.5%, 3.2% and 3.5% for the completed rounds 1, 2 and 3, respectively, in all five centres. Incidence of high grade PIN increased from 1.5% in the first round to 5.0% in the third round, varying among centres in the first round between 0.8% and 7.6%. The cancer detection rate in the first re-biopsy after the diagnosis of high grade PIN was 12.9%. Incidence of LSPC was 2.4%, 2.7%, 2.2% and 2.6% in the first, second, third and fourth round, respectively. The cancer detection rate at the first re-biopsy after the diagnosis of LSPC was in average 33.8%.

Conclusions: Cancer detection rate was stable during the three screening rounds. The wide variation in frequency in particular of high grade PIN among the ERSPC centres suggests a

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.09.035

considerable inter-observer variation. The average comparatively low detection rate of isolated high grade PIN in the first screening round may be screening-related, while its consistent increase during three screening rounds could be the consequence of a.o. previous screening and ageing of the population. The observed low risk of prostate cancer after isolated high grade PIN in this screening setting is in line with the current recommendation to abstain from early repeat biopsies after this diagnosis. The association of LSPC with high incidence of prostate cancer in re-biopsies confirms the need for early repeat biopsies and follow-up of these men. The low percentage of LSPC (<3% of biopsies) throughout all rounds is reassuring as it limits the biopsy burden in a screening setting.

1. Introduction

High grade prostatic intraepithelial neoplasia (PIN) is a neoplastic transformation of superficial secretory epithelial cells of prostatic ducts and glands, characterised by cell atypia, prominent nucleoli, secretory cell proliferation and interruption of basal cell layer in architecturally benign glands.[1,2] High grade PIN is generally considered as a precancerous state for prostate cancer, while detectable in at least 70% of prostatectomies containing a prostate cancer.[2–4] The prevalence of isolated high grade PIN in prostate biopsies is reported to show wide variation in the earlier studies. The mean reported incidence of isolated high grade PIN was 9%,[3,4] showing variation from 4.4% to 25% in biopsies from urological practice.[4] Lower prevalence of PIN in prostate biopsies has been reported along with increased use of PSA-testing,[5] as well as during the PSA screening in one screening centre.[6] The clinical significance of isolated high grade PIN is based on the demonstration in older studies of a high risk of subsequent prostate cancer in follow-up biopsies.[5,7] These data have been mainly obtained from studies of non-screened populations. Based on these studies early re-biopsy was recommended for patients with high grade PIN,[4] and this recommendation has been followed also in the screening centres. As a consequence a substantial proportion of asymptomatic men screened for prostate cancer needed to undergo an additional biopsy, which is undesirable in a screening setting. However, the reported predictive value of PIN for subsequent carcinoma has decreased during the last years.[6,8] Particularly, studies comparing the incidence of prostate cancer after an initial diagnosis of isolated high grade PIN with that after a benign biopsy diagnosis did not reveal significant differences.[5,7]

Lesions suspicious for but not diagnostic of prostate cancer and LSPC have also been called glandular atypia or more commonly ASAP (atypical small acinar proliferation).[8] Difficulties to render a definitive diagnosis of cancer in case of small atypical lesions have been shown recently.[9] Suspicious lesions have been followed by much higher cancer detection rates than PIN,[5,6,8] and therefore a re-biopsy has often been recommended by pathologists after LSPC diagnosis.

In the present study the detection rates for prostate cancer, PIN and LSPC in five centres of ERSPC study were determined. A further aim of the study is to identify changes in their incidences during subsequent screening rounds and the risk of cancer detection in subsequent prostate biopsies.

2. Material and methods

2.1. Participating ERSPC centres

In the European Randomized Study of Screening for Prostate Cancer, 182,000 men aged 51–75 years were randomised in a screening arm and a control arm in eight countries. Study group of the present study consists of 56,653 screened men in five ERSPC centres, Finland, Italy, Netherlands, Sweden and Switzerland, who underwent 3–7 screening rounds. Age range at entry was 51–66 years in Sweden, 55–67 years in Finland, 55–75 years in the Netherlands and Italy and 55–69 years in Switzerland. Indications for prostate biopsy varied between centres. Most centres used PSA 3 or over or positive digital rectal examination, or positive transrectal ultrasonography as an indication for biopsy. PSA over 4 was used in Finland and Italy. In Finland PSA values 3–4 combined with percentage of free to total PSA 0.16 or higher were also indications for biopsy from year 1997 onwards. Screening interval varied from 2 years in Sweden to 4 years in other four participating centres. Sextant prostate biopsy was used except in Finland, where a policy of 10–12 biopsies was adapted during the second round, from year 2002 onwards. According to the protocol, an early repeat biopsy within 6 months was recommended following a diagnosis of isolated high grade PIN and/or LSPC.[10]

2.2. Cancer, high grade PIN and LSPC detection

Prostate biopsies were examined by local pathologists of the participating ERSPC centres. Data for cancer detection during screening have been obtained from central database. Cancer detection rates were available for the completed first three screening rounds of each of the centres which contributed data for this paper.

PIN diagnosis is used as the synonym for high grade PIN. Only isolated high grade PIN is recorded, high grade PIN diagnosis in connection with cancer was not included. LSPC included cancer suspicions, diagnosis of ASAP (atypical small acinar proliferation) and atypias followed by control biopsy. If a high grade PIN diagnosis was given in connection with LSPC, the biopsy diagnosis was recorded as LSPC.

The data for high grade PIN and LSPC have not been recorded uniformly in the central database, and therefore incidence data for PIN and LSPC were obtained directly from individual centres in the five countries. In some centres high

grade PIN and LSPC could be obtained only for part of the biopsies. Data for high grade PIN were not available for the three first rounds in Sweden and data for high grade PIN and LSPC were missing for the third round in Switzerland. Detection rates of prostate cancer subsequent to PIN and LSPC diagnoses were evaluated only for the first re-biopsy.

3. Results

Average cancer detection rate in the screening arm of the five centres combined during the three first rounds was 3.5%, 3.2% and 3.5% in the first, second and third rounds, respectively (Table 1). Data were based on 17,864 biopsies, from which 4178 cancers were detected – that is an average positive biopsy percentage for all three rounds in the five centres of 23.4% and cancer detection rate of 3.4% (data not shown). When we compare the cancer detection rates per screening round in each of the five centres, only slight fluctuation was found between the rounds. Both the detection rate of cancer and the percentage of biopsies with cancer were very low in Italy. In Sweden, with a screening interval of 2 years and a lower age range as compared to the other centres, the cancer detection rate in the fourth round to seventh round was 2.4%, 4.2% and 3.2%, respectively (data not shown). The detection rate for the fourth round in Netherlands was 3.5% (data not shown).

The data for isolated high grade PIN gathered from four centres are listed in Table 2. The rate of high grade PIN from the biopsies varied in the first round from 0.8% in the Netherlands to 7.6% in Italy. Detection rates of high grade PIN increased during the second and the third rounds in the Netherlands, Finland and Switzerland, but not in Italy. In the Netherlands a decrease was noted during the incomplete fourth round. In Sweden the rate of PIN during rounds 4–7

Table 1 – Assessment, biopsy and cancer at regular screening rounds (R) 1–3, without delayed or repeat screens.

ERSPC centre	Number of men screened			Cancer, percentage of biopsies			Cancer detection rate, percentage of screened		
	R1	R2	R3	R1	R2	R3	R1	R2	R3
Netherlands	19,970	12,531	7712	24.6	18.9	19.3	5.1	4.4	4.1
Finland	20,789	16,245	10,262	29.2	28.3	30.9	2.6	3.2	3.4
Italy	5106	3903	2598	17.4	18.9	18.1	1.6	1.4	1.0
Sweden	5855	4684	2282	23.7	21.0	19.2	2.4	2.0	4.7
Switzerland	4933	4276	2103	18.8	21.2	24.8	3.6	3.1	3.8
Total	56,653	41,639	24,957	24.5	22.1	23.1	3.5	3.2	3.5

Data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) central database in November 2009.

Table 2 – Detection rates of prostatic intraepithelial neoplasia (PIN) during screening rounds (R).

ERSPC centre	Number of biopsies (*n*)			Number of PIN (*n*)			PIN, percentage of biopsies (%)		
	R1	R2	R3	R1	R2	R3	R1	R2	R3
Netherlands	4117	1840	1671	34	46	55	0.8	2.5	3.3
Finland	2814	3325	1930	36	99	124	2.3	3.0	6.4
Italy	484	343	183	37	20	10	7.6	5.8	5.5
Switzerland	625	552	NA	10	22	NA	1.6	2.3	NA
Total	8040	6060	3784	117	187	189	1.5	3.1	5.0

NA = not available.

Table 3 – Detection rates of lesions suspicious for prostate cancer (LSPC) during screening rounds (R).

ERSPC centre	Number of biopsies (*n*)				Number of LSPC (*n*)				LSPC, percentage of biopsies (%)			
	R1	R2	R3	R4	R1	R2	R3	R4	R1	R2	R3	R4
Netherlands	4117	1840	1671	690	108	50	35	15	2.6	2.7	2.1	2.2
Finland	2814	3325	1930	SC	74	96	36	SC	2.6	2.9	1.9	SC
Italy	484	343	183	SC	1	1	1	SC	0.2	0.3	0.6	SC
Sweden	595	508	737	629	5	11	29	19	0.8	2.2	3.9	3.0
Switzerland	625	552	NA	SC	18	16	NA	SC	3.0	3.0	NA	SC
Total	8635	6568	4521	1319	206	174	101	34	2.4	2.7	2.2	2.6

NA = data not available.
SC = screening completed.

Table 4 – Cancer detection in the control biopsy after prostatic intraepithelial neoplasia (PIN) or lesions suspicious for prostate cancer (LSPC).

ERSPC centre, round	PIN (*n*)	Cancer after PIN (*n*)	Cancer (%)	LSPC (*n*)	Cancer after LSPC (*n*)	Cancer (%)
Netherlands, 1st round	34	4	11.8	108	35	36.5
Netherlands, 2nd round	46	6	13.0	50	8	16.0
Netherlands, 3rd round	55	8	14.5	35	9	25.7
Netherlands, 4th round	11	3	27.3	15	7	46.7
Switzerland, 1st round	10	2	20.0	18	6	33.3
Switzerland, 2nd round	22	0	0.0	16	5	31.3
Finland, 1st round	36	10	27.8	74	31	41.9
Finland, 2nd round	99	13	13.1	96	34	35.4
Finland, 3rd round	124	13	10.5	36	11	30.6
Sweden[a]	122	17	13.9	131	50	38.0
Italy[b]	67	5	7.5	3	1	33.3
Total	626	81	12.9	582	197	33.8

ERSPC the European Randomized Study of Screening for Prostate Cancer.

Statistical test on prostate cancer detection rates (Pearson chi-squared test): cancer after LSPC versus cancer after PIN $p < 0.0001$.

[a] Data of Sweden contains PIN cases combined from rounds 4 to 7 and LSPC cases combined from all rounds.

[b] Data of Italy contains PIN and LSPC cases combined from rounds 1 to 3.

varied and the overall average was 5.4% (data not shown). In average, the detection rate of high grade PIN increased during the first three screening rounds from 1.5% in the first round to 3.1% in the second round and to 5.0% in the third round.

The frequency of LSPC in the five screening centres for the subsequent screening rounds is listed in Table 3. On the average the rate of LSPC remained fairly constant during the three rounds, ranging from 2.4% in the first round to 2.2% in the third round (Table 3). In Italy, the percentage for LSPC was very low in all rounds ranging from 0.2% to 0.6%, and in Sweden only in the first round 0.8%. During rounds five to seven in Sweden the detection rates were 4.6%, 4.7% and 2.8% (data not shown).

Follow-up biopsies after an initial diagnosis of high grade PIN lesions showed that percentage of cancers found in the re-biopsy was 12.9% (Table 4). The percentage of cancer in repeat biopsies after LSPC was 33.8% (Table 4) (Pearson chi-square test $p < 0.0001$). The percentage of cancer detection was consistently higher after LSPC than after high grade PIN in all centres and during all screening rounds.

4. Discussion

The rate of cancer detection in the present study was fairly stable during the three rounds, although there was considerable variation between the centres. The rate was lowest in Italy. Reasons for the difference between centres may be due to many factors, for example the comparatively low biopsy compliance in Italy as reported previously.[11] The average detection rate of prostate cancer (3.4%) in the five screening centres is higher than the general detection rate in these countries (from 0.8% to 1.6%) as shown by Bray et al.[12] Previously it was shown that cancers detected in subsequent screening rounds as well as interval cancers had a reduced extent of cancer and lower Gleason score in the biopsies.[13,14] Taken together, these observations would suggest that after depletion of the larger tumours during the prevalence screening the screening interval of 2–4 years allows the appearance of a new population of small PSA screening detectable cancers, while the time interval is insufficient for most cancers to grow large.

In the present study, the overall detection rate of isolated high grade PIN was low. It was even lower than its expected detection rate between 5% and 8% reported in other recent studies.[5] The low rate may be related to the screening setting which is different from clinical cancer setting, even though PSA-testing is very common also in clinical practice. Increase in high grade PIN detection rate was found during subsequent screening rounds, and in the largest centres Finland and Netherlands, this increase in high grade PIN was noted from round 1 to 3. Ageing of the screened men may offer some explanation for this, because increase of high grade PIN with age has been shown in previous studies[4] and our findings were not corrected for age. The fairly large increase in the rate of high grade PIN in Finland during subsequent screening rounds may partly be also due to the change in the biopsy protocol during the second round from sextant biopsies to 10–12 biopsies. This change was done along with changed biopsy policy in clinical practice. Preliminary data suggest that larger biopsy number is associated with increased detection rate of high grade PIN (data not shown). In Italy, where the PIN detection rate during the prevalence screening was highest, no further increase was found during the following rounds.

There may also be differences in diagnosis of high grade PIN between centres. This could be studied further by re-evaluation of the PIN diagnoses. High rate of over-diagnosis of PIN has been shown in review of PIN cases by Bostwick and Ma.[15] On the other hand, the criteria for diagnosis and reporting of PIN have been shown to be fairly uniform among uropathologists.[16]

The existing guidelines for prostate biopsies during screening[10] recommend re-biopsy in cases of isolated high grade PIN within 6 months. However, in Italy this guideline was not generally applied and also in other centres the time interval from initial biopsy to the first re-biopsy was some-

times longer than 6 months. In all centres the re-biopsy data showed low frequency of cancer in the first re-biopsy after high grade PIN. Indeed, the risk of cancer detection after isolated high grade PIN is essentially the same as after an initial benign diagnosis (<15%).[6,7] These data are comparable to other recent studies[2,5,6] and support the suggested guidelines, i.e. in the absence of clinical cancer suspicion; PIN finding needs no early re-biopsy at least within the first year after the diagnosis.[5] In the present study, further follow-up of the patients after the first re-biopsy has not been included, neither the follow-up of men who did not come to the first re-biopsy. Nevertheless, the existing ERSPC material gives an opportunity to further follow-up of men with diagnosis of isolated high grade PIN during later screening rounds and even after the screening trial. Therefore the screening trial will hopefully give further information about the question of preneoplastic role and clinical importance of isolated high grade PIN during a longer period. So far, the role of PIN as a preneoplastic change has been based on studies of clinical urology practice and long-term follow-up data during the PSA-era are few.[17] A limitation of this study is that we did not evaluate the extent of PIN, which according to a recent study may be associated with a slightly increased risk of subsequent cancer detection.[18]

In spite of the potential for considerable variation in diagnostic opinion, even among well-established uropathologists,[9] the rate of LSPC lesions was constant between the countries, with the exception of Italy, where suspicious lesions were diagnosed very seldom. Further, the ERSPC average percentage around 2.5% compares well with and is even lower than that reported previously in the literature.[5] This is somewhat unexpected, since in a screening setting cancers are likely of smaller size, particularly in subsequent screening rounds, and therefore an increased number of atypical foci, falling short of a definite diagnosis of cancer, was anticipated. The application of immunohistochemical stains by the screening centres may have limited the frequency of LSPC and helped to make a diagnosis of cancer. About a third of suspicious lesions were followed by cancer in re-biopsy, which is well in line with earlier studies.[2,5] This percentage remained high in all rounds, except during the second round in the Netherlands, which was shown already earlier.[6] The present data confirm that an early re-biopsy after a suspicious lesion is indicated.

In spite of variation in the reporting and diagnostics of isolated high grade PIN and LSPC, the data support the opinion that PIN diagnosis in a screening setting does not need immediate re-biopsy, whereas early re-biopsy after a diagnosis of suspicious lesion is needed. In conclusion, the need for early re-biopsy in asymptomatic men in a screening setting appears to be limited to about 3% of the men with an elevated PSA, and fortunately thus represents a minor burden of the screening process.

Conflict of interest statement

None declared.

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