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Gleason score, age and screening: Modeling dedifferentiation in prostate cancer

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Tumor differentiation as measured by the Gleason score is highly predictive of the course of prostatic cancer after diagnosis. Since the introduction of the prostate-specific antigen (PSA) test tumors are diagnosed with a favorable tumor stage and differentiation grade. Does screening with PSA just detect more tumors with favorable characteristics or is dedifferentiation actually being prevented by early detection and consequent treatment? The latter option implies that tumors dedifferentiate in the preclinical screen-detectable phase. To model the natural history of prostate cancer, we analyzed the age-specific distribution of clinical stage and Gleason score of 2,204 tumors diagnosed in the ERSPC-Rotterdam trial. We fitted 2 MISCAN simulation models to the observed data: Model I where tumors dedifferentiate before becoming screen-detectable and Model II where dedifferentiation occurs during the screen-detectable preclinical phase. The hypothesis of dedifferentiation during the screen-detectable phase was tested by a goodness of fit test of both models. In ERSPC-Rotterdam, we observed a significantly more favorable distribution of Gleason scores in screen-detected cancers compared to cancers found in the control arm, and in cancers detected in the second round compared to cancers detected in the first round of screening. Also, a significant association between Gleason score and age at diagnosis was found, most notably in cancers detected in the first round of screening. These findings were reproduced by Model II and less so by Model I, with a significant difference in goodness of fit between the 2 models ($p < 0.001$).This study provides epidemiological evidence of dedifferentiation as a major mechanism of progression in prostate cancer. Tumors dedifferentiate during the screen-detectable phase and consequently screening with PSA and early treatment can possibly prevent dedifferentiation.

Key words: prostatic neoplasms; Gleason score; screening; computer simulation; aging

In the western world the incidence of prostate cancer is increasing because of the general availability of serum tests for prostate specific antigen (PSA) and aging of the population.[1] Early detection by PSA testing and curative treatment of prostate cancer may result in a decrease in mortality from prostate cancer,[2] but definite evidence for this effect is not yet given. Nevertheless, trial results show that TNM stage and Gleason score of screen-detected tumors compare favorably to those of clinically diagnosed tumors in the control arms of the trials[3,4]; in particular Gleason score is predictive for treatment success and survival.[5] It is tempting to deduce that early detection by screening and treatment could prevent tumor growth and dedifferentiation. However, the favorable characteristics of screen-detected cancers might be due to length bias sampling: tumors with favorable characteristics probably grow more slowly and have more chance of being detected; moreover, these tumors might never give rise to clinical symptoms and therefore not show up in unscreened/nonscreened populations.[6] Concentrating on Gleason score, our question is: Does screening with PSA just detect more tumors with favorable characteristics or is dedifferentiation actually being prevented by early detection and consequent treatment?

Screening can only prevent dedifferentiation if it occurs in cancers that are detectable by the screening test: screening cannot affect dedifferentiation that has taken place before the tumor has become screen-detectable. Dedifferentiation in the screen-detectable phase is supported by a recent publication of Johansson *et al.*[5] who followed 223 prostate cancer patients managed by watchful waiting. Using the WHO grading system they observed dedifferentiation in 31 (17%) out of 178 patients for whom repeat biopsies were available. Epstein *et al.*[7] also noted dedifferentiation in 9 out of 70 patients followed by watchful waiting, but because of the small number of cases, and the short time between successive biopsies the authors suggested biopsy variability as the cause of the observed change of the Gleason score. On the other hand, Thompson *et al.*[8] reported a detection rate of prostate cancer of 15% in men with PSA levels below a cut-off point of 4 ng/ml. In these men 15% Gleason scores $\geq$7 were found, suggesting that high Gleason scores already exist before a tumor becomes detectable by PSA screening. Also the widespread screening with PSA in the United States has caused a shift to earlier-stage disease, and a markedly lower incidence of distant disease, but it has not lead to a shift to lower grade disease.[9]

This study aims at modeling the natural history and dedifferentiation of prostate cancer using detailed information from 2,204 cancers diagnosed in the Rotterdam center of the European Randomized study of Screening for Prostate Cancer (ERSPC-Rotterdam). We investigated whether our data show a relation between Gleason score, clinical T-stage (cT-stage) and age at diagnosis as noted by others.[10,11] We used the findings to discriminate between 2 MISCAN simulation models that do not allow (Model I) or do allow (Model II) dedifferentiation in the screen-detectable phase. A significantly better fit to observed data of Model II is a strong indication of dedifferentiation that could be prevented by early detection and treatment.

Patients and methods

Patients and screening strategies

In ERSPC-Rotterdam, 42,376 men, 55–75 years old, were randomized to a screening (n = 21,210) and a control arm (n = 21,166). Ethical approval of the study was obtained from the Dutch ministry of health (committee on the population screening act, WBO committee no. 325291). In the first screening round (November 1993–December 1999) the screening test initially consisted of PSA determination, digital rectal examination (DRE) and transrectal ultrasonography (TRUS). Sextant needle biopsy was recommended for participants who had an elevated PSA level ($\geq$4.0 ng/ml), abnormal DRE or abnormal findings on TRUS. Men with a benign biopsy result in the first round were invited for a recall visit after 1 year (early recall visits). The protocol was simplified in May 1997, when sextant biopsy was recommended if PSA was $\geq$3.0 ng/ml, regardless of DRE and TRUS.[12] During the second screening round (June 1998–December 2003), performed 4 years after the first screening round, the PSA $\geq$3.0 ng/ml protocol was used. Diagnoses of prostate cancer in men in the control arm and in the screen arm but outside the screening program were obtained through record linkage with the Dutch cancer registry (100% coverage). The registry and subsequent linkage leads to a

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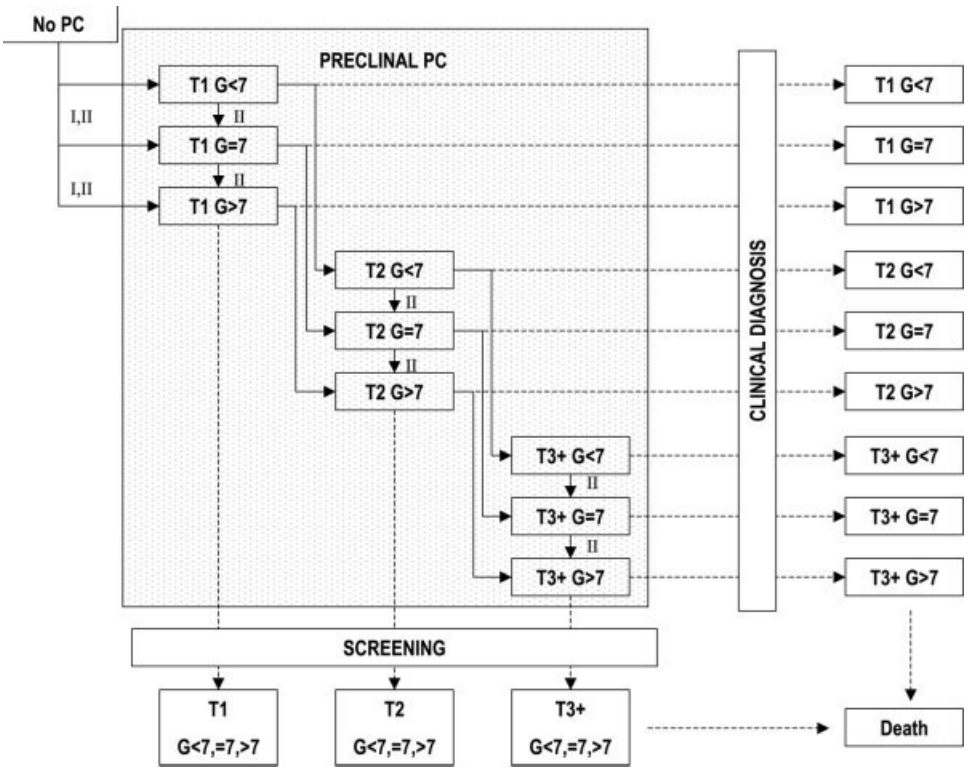

FIGURE 1 – The MISCAN prostate cancer model. Prostate cancer develops from no cancer *via* 1 or more screen-detectable preclinical stages to a clinically diagnosed tumor. In each preclinical state a tumor may grow to the next T-stage, dedifferentiate to a higher Gleason score or give rise to symptoms and be clinically diagnosed. For these transitions the time spent in the current state is generated from a Weibull distribution (2 parameters) and the choice of the next state is determined by transition probabilities (2, 1 or 0 parameters, dependent on the current state). Screening—superimposed on life histories without screening—may detect tumors earlier in one of the preclinical stages; detection depends on stage-specific sensitivities of the screening test. Transitions that represent dedifferentiation to a higher Gleason score are labeled I and/or II, indicating whether the transition is allowed in the corresponding model. Model I allows dedifferentiation only before the preclinical detectable phase; model II allows dedifferentiation before and in the preclinical phase. Transitions are prohibited by assigning a zero value to the corresponding probability.

delay of 1–2 years in the reporting of these tumors. In this study we used a cut-off date of July 2, 2002 for inclusion of cancers diagnosed outside the trial screening program.

Pathologic processing

Slides from prostate biopsies, transurethral resection of the prostate (TURP) and prostatectomy specimens were retrieved from the archives of the pathology laboratories of the Erasmus MC and surrounding hospitals of the Rotterdam region. Biopsies from the surrounding hospitals varied from 2 to 12 cores per biopsy. One uropathologist (T.H.vd K.) reviewed all biopsies with cancer, PIN and lesions suspicious for malignancy so as to avoid inter-observer variation. The grading of prostate cancer used in the ERSPC is the Gleason score system,[13] which is based on growth patterns present in the tumor, classified from pattern 1 to 5. The Gleason score system combines the 2 most prominent patterns. Therefore Gleason scores range from 2 to 10, with score 2 indicating the best differentiated tumors and score 10 the poorest. Tumors with Gleason score 2–6 are considered low grade, with 7 intermediate grade and with Gleason score 8–10 high grade. Internationally it is agreed that a needle biopsy is not graded under Gleason score 6.[14] Gleason scores are missing for 4 patients from the first screening round and for 56 patients in the control arm. As control arm biopsies were reviewed at random, no bias due to missing scores is to be expected.

MISCAN modeling and statistical analysis

The MISCAN prostate model has been described earlier.[6] In short, MISCAN is a microsimulation program, which simulates the development of prostate cancer in individual men as a sequence of tumor states (Fig. 1). The states are characterized by T-stage (T1, impalpable; T2, palpable, confined to the prostate; and T3+, palpable, with extensions beyond the prostatic capsule[15]) and differentiation grade (low, Gleason score 2–6; intermediate, Gleason score 7; and high grade, Gleason score 8–10). Technically, MISCAN implements a semi-Markov model. Parameters in this model are probabilities of transitions between states, distribution of the times spent in each state and sensitivities of the screening test (Fig. 1). All parameters of the models in this article were estimated by numerical minimization of the deviance between observed data and corresponding model predictions. We used the following data: age-specific incidence at baseline before the introduction of the PSA test (National Cancer Registry (NCR) data for 1991[16]); age-specific cT-stage distribution at baseline (Rotterdam cancer registry data 1992/3[17]); age-specific incidence or detection rates and joint distribution of cT-stage and Gleason score in the control arm of the ERSPC-Rotterdam (data up to July 2002) and first and second screening round in the screened arm; finally incidence and joint distribution of cT-stage and Gleason score of the interval cancers by time since last negative screening test. For modeling purposes, cases detected in the early recall visits that were part of the initial screening protocol were counted as being detected in the first screening round. For cancers in the control arm and interval cancers we used a cut-off date of July 2, 2002 for inclusion and calculating men-years.

To answer the research question of this study, we constructed 2 MISCAN models: in Model I the differentiation grade is determined before entering the preclinical screen-detectable phase and

TABLE I – GLEASON SCORES BY AGE AT DIAGNOSIS OF CANCERS AND DETECTION MODE DIAGNOSED IN ERSPC-ROTTERDAM

Study group	Age group	Gleason score								Total *n*	Rate[1]
		<7		=7		>7		Unknown			
		N	%[2]	*N*	%[2]	*n*	%[2]	*n*	%[3]		
Control arm[4,5]	55–59	19	67.9	4	14.3	5	17.9	1	3.6	29	1.7
	60–64	37	50.7	17	23.3	19	26.0	9	12.3	82	2.7
	65–69	53	41.7	46	36.2	28	22.0	10	7.9	137	5.1
	70–74	57	42.9	40	30.1	36	27.1	20	15.0	153	6.7
	75+	26	46.4	17	30.4	13	23.2	16	28.6	72	8.3
	Total	*192*	*46.0*	*124*	*29.7*	*101*	*24.2*	*56*	*13.4*	*473*	*4.5*
Screen arm											
Round 1	55–59	125	75.8	31	18.8	9	5.5	1	0.6	166	28[6]
	60–64	161	70.6	56	24.6	11	4.8	0	0.0	228	45
	65–69	212	60.9	107	30.7	29	8.3	2	0.6	350	77
	70–74	148	56.5	82	31.3	32	12.2	0	0.0	262	87
	75+	4	66.7	1	16.7	1	16.7	1	16.7	7	167
	Total	*650*	*64.4*	*277*	*27.5*	*82*	*8.1*	*4*	*0.4*	*1013*	*54*
Early recalls	55–59	8	80.0	1	10.0	1	10.0			10	
	60–64	8	72.7	3	27.3	0	0.0			11	
	65–69	13	81.3	3	18.8	0	0.0			16	
	70–74	18	72.0	7	28.0	0	0.0			25	
	75+	3	100.0	0	0.0	0	0.0			3	
	Total	*50*	*76.9*	*14*	*21.5*	*1*	*1.5*			*65*	
Round 2	55–59	15	75.0	5	25.0	0	0.0			20	21
	60–64	139	81.3	27	15.8	5	2.9			171	29
	65–69	146	77.2	36	19.0	7	3.7			189	49
	70–74	135	79.4	30	17.6	5	2.9			170	72
	Total	*435*	*79.1*	*98*	*17.8*	*17*	*3.1*			*550*	*44*

[1]The rate was in terms of incidence per 10^3 men-years for control arm and detection per 10^3 tests for screen arm.–[2]Percentage of cases with Gleason score known.–[3]Percentage of total cases.–[4]Including Gleason scores of 33 TURP specimens and 6 prostatectomy specimens.–[5]Follow-up up to July 2002.–[6]Including cancers detected by early recalls.

it does not change afterwards; in Model II dedifferentiation may also occur in the screen-detectable phase. Technically this was achieved by fixing the 6 transition probabilities to a higher grade in the preclinical phase at zero in Model I (see also Fig. 1) and estimating them from the data in Model II. All other parameters were allowed to vary in both models, and were estimated from the data as described above. Thus, we estimated a total of 39 parameters in Model II and 33 (39 − 6) in Model I. As Model I is a nested model with respect to Model II, we used a likelihood ratio test to decide whether the deviance-based goodness of fit of Model II was significantly better than that of Model I.

Ordinal regression[18] was used to test the significance of the shift towards lower grade in screen-detected cancers compared to cancers in the control arm and the significance of the association between grade and age at diagnosis.

TABLE II – ORDINAL REGRESSION MODELING THE EFFECTS OF DETECTION MODE AND AGE ON TUMOR DIFFERENTIATION CATEGORIZED AS WELL (GLEASON < 7), MODERATELY (GLEASON = 7) AND POORLY DIFFERENTIATED (GLEASON > 7)

	Hazard ratio[1]	*p*-value
Detection mode		
Diagnosed in control arm	1.0	
Detected in screened arm	0.59	<0.001
Detected in screened arm, round 2	0.69	<0.001[2]
Age per 10 years increase		
Overall	1.25	<0.001
Detected in screened arm, round 1	1.35	<0.001
Diagnosed in control arm	1.10	0.09[2]
Detected in screened arm, round 2	1.11	0.1[2]

[1]The hazard ratio relates to the hazard of transition to the next higher Gleason category before being diagnosed.–[2]*p*-Value refers to the difference from round 1 hazard ratio.

Results

Prostate cancer incidence

In ERSPC-Rotterdam, 19,970 men were screened in the first round and 1,013 cancers detected (detection rate 5.1%); if we include the 65 cancers found at the early recall visits, in total 1,078 cancers were found in the first round (detection rate 5.4%). In the second round 12,529 men were screened and 550 cancers detected (detection rate 4.5%), of which 393 before July 2002. Up to July 2002, 473 men were diagnosed with cancer in the control arm, and 103 interval cancers were found in the screening arm, *i.e.*, diagnosed outside the screening program after a negative screening test. Cumulative incidence in July 2002 after a mean follow-up of 5 years was 7.5% in the screened arm and 2.2% in the control arm.

Gleason scores

The differentiation grade of screen-detected cancers (70% low grade = Gleason score 2–6 and 6% high grade = Gleason score 8–10) is more favorable than that of cancers diagnosed in the control arm (46% low; 24% high) and more favorable in the second round (79% low; 3% high) than in the first round of screening (65%low; 8% high) (Table I). The figures for the control arm include Gleason scores based on material obtained by TURP (33 cases) or prostatectomy specimens (6 cases) of patients treated for bladder cancer or benign hyperplasia. Excluding these cases for which no biopsy grade was available, affected the grade distribution only slightly (43% low and 25% high grade). Ordinal regression showed that the shift towards more favorable Gleason scores in screen-detected cancers and from first to second round is significant ($p \leq 0.001$, see Table II). Nevertheless, in July 2002, after a mean follow-up of 5 years, the total number of patients with high-grade prostate cancer was equal (101) in both arms of the trial.

Older men have higher Gleason scores (Table I and Fig. 2). Ordinal regression showed that the relation is significant with a hazard ratio of 1.25 per 10 years of age increase (Table II). The analysis also suggested that the relation is strongest in tumors detected in the first round of screening, but the difference in hazard ratios between the 3 modes of detection was not statistically significant ($p = 0.09$–0.12). There was no significant relation between cT-stage and age, neither in the screening arm nor in the control arm

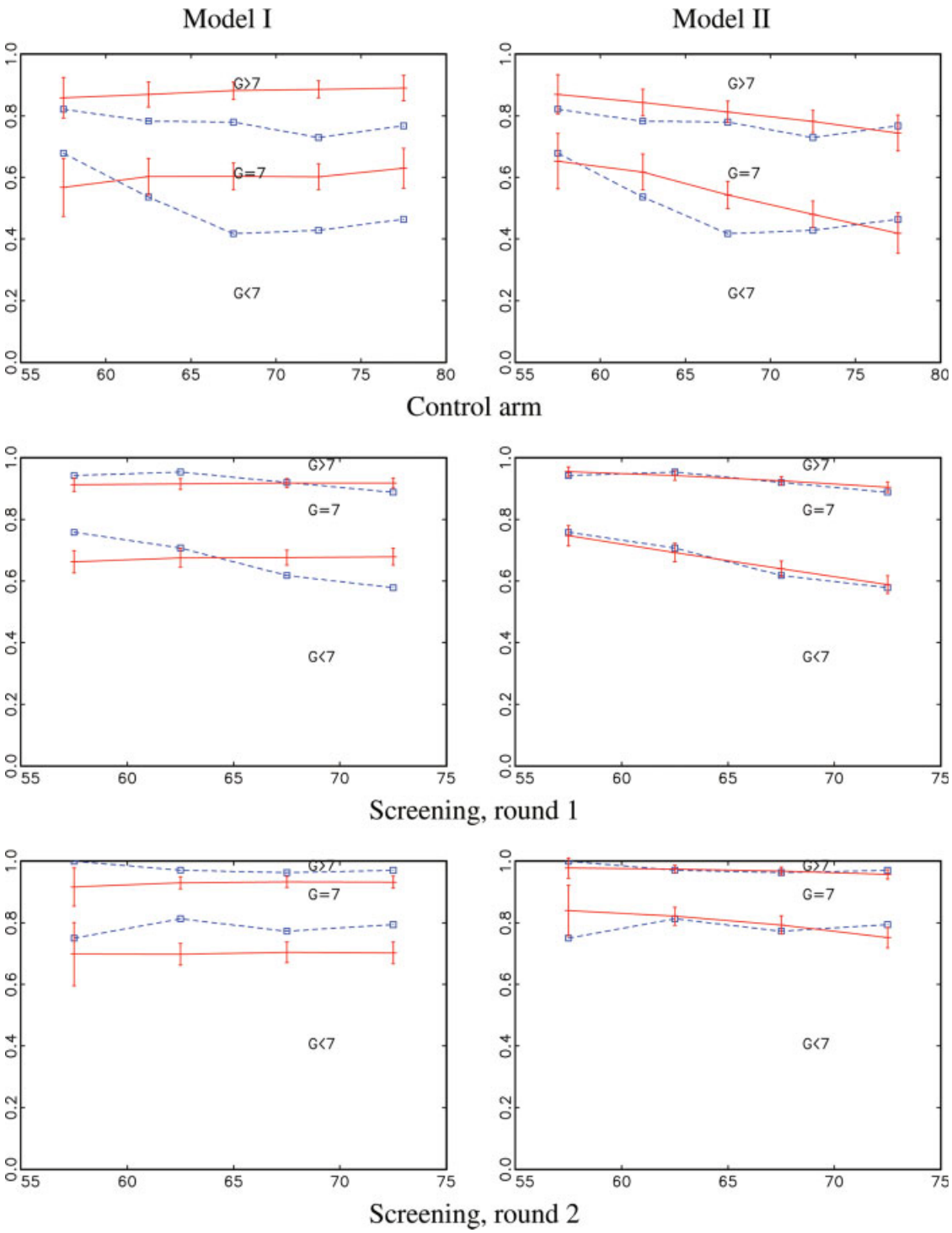

FIGURE 2 – Gleason score by 5-year age group and study population as observed and predicted by a model without (Model I) dedifferentiation in the screen-detectable phase and a model with (Model II). The graphs indicate the cumulative proportions of Gleason scores less than 7 and less than or equal to 7. The dashed lines indicate the observed distribution, and the solid lines indicate the predicted distribution. Error bars indicate the standard error of the predicted fractions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(data not shown); also, correcting for cT-stage did not affect the relation between age and Gleason score.

Modeling

Table III compares the observed cT-stage and grade distributions with the predictions from Models I and II. Both models accurately predict the clinical stage distribution of tumors detected by screening in the first and second round. However the models predict a more favorable distribution than that observed at baseline, and a less favorable distribution than that observed in the control arm and interval cancers. Both models reproduce the grade distribution observed in tumors detected in the first round of screening, but Model II reproduces the observed differences between the var-

TABLE III – OBSERVED PERCENTAGE DISTRIBUTION OF CLINICAL T-STAGE AND GLEASON SCORE IN ERSPC-ROTTERDAM AS OBSERVED AND PREDICTED BY MISCAN MODEL I (NO DEDIFFERENTIATION IN DETECTABLE PRECLINICAL PHASE) AND MODEL II (DEDIFFERENTIATION IN PRECLINICAL PHASE)

Population	CT-stage				Gleason score			
	n	T1 (%)	T2 (%)	T3+ (%)	*N*	G < 7 (%)	G = 7 (%)	G > 7 (%)
Observed								
Baseline 1992/3	1610	14	59	27				
Control arm[12]	349	42	31	28	417	46	30	23
Screen arm round 1	1078	36	46	18	1074	65	27	8
Screen arm round 2	550	62	35	4	550	79	18	3
Screen arm interval cancers[2]	92	59	26	15	40	72	16	13
Model I								
Baseline 1992/3		18	53	28				
Control arm		27	50	23		60	28	12
Screen arm round 1		40	44	16		67	24	8
Screen arm round 2		59	34	7		70	23	7
Screen arm interval cancers		35	53	12		65	24	11
Model II								
Baseline 1992/3		20	52	28				
Control arm		28	49	23		53	28	20
Screen arm round 1		39	45	16		65	27	7
Screen arm round 2		61	34	5		79	18	3
Screen arm interval cancers		43	45	12		60	21	19

[1]Including Gleason scores of 33 TURP specimens and 6 prostatectomy specimens.–[2]Follow-up up to July 2002.

ious study groups more closely than Model I. Note however, that Model I does allow a modest shift to a more favorable grade distribution in screen-detected cancers.

The observed relation between age and grade is predicted by Model II, but not by Model I (Fig. 2). Model II fitted the data significantly better than Model I (difference in deviance of 100 with 6 extra parameters; $p < 0.001$).

Discussion

Prostate cancer is a heterogeneous and often multifocal cancer, which is marked by different Gleason patterns in 1 tumor. Two mechanisms can explain the presence of high-grade and low-grade components in prostatic tumors: (*i*) the different grades are present at the time of tumor initiation due to the presence of pluripotent stem cells that shed throughout the prostate and grow in different sites of the prostate to form a heterogeneous cancer[19] or (*ii*) prostatic tumors dedifferentiate during their development and progress from low grade to high grade. In the first case Gleason score is determined early in the development of the tumor. Both mechanisms might also occur at the same time.

Our findings support the second mechanism: progressive dedifferentiation. Our Model I, assuming predetermined differentiation grades, did predict a modest shift towards lower grades in screen-detected tumors compared to clinically diagnosed cancers but the predicted shift was too small, and the model did not predict the observed association with age. Model II, allowing dedifferentiation in the screen-detectable phase, fitted the observed data significantly better. In this model early detection may prevent dedifferentiation, explaining the observed shift to lower grade in screen-detected cancers compared to cancers diagnosed in the control arm. In the first round of screening, tumors detected in older men have had a longer time of development and consequently more chance to dedifferentiate. In the second round, many tumors developed since the last screening test and consequently had lower Gleason scores and the relation with age is less clear. The high percentage (80%) of low-grade tumors in round 2 suggests that few tumors progress to a higher grade within the 4-year screening interval.

The finding that older men have more poorly differentiated prostate cancers than younger men has been reported before.[10,11] Several authors studied dedifferentiation by comparing differentiation in metastases and primary tumors[20,21] and concluded that there is a trend toward histological dedifferentiation when prostate carcinoma metastasizes to regional lymph nodes. It could be argued however, that these observations are the consequence of a higher potential for metastasis of poorly differentiated tumor cells, rather than dedifferentiation.

Repeated samples in time from individual patients are the most direct way to study dedifferentiation. An early study of Brawn in 1983[22] reported dedifferentiation between 2 subsequent TURP specimens with an interval of 3–11 years, in 65% of 54 patients; in the remaining 33% no substantial difference in differentiation grade was found (Anderson score was used). In this study, the majority of patients received hormone therapy, which may artificially produce the appearance of a higher prostate cancer grade.[23] Another study reported dedifferentiation in 68% of tumors not treated with hormones between 2 subsequent TURP procedures with a mean interval of 2.4 years.[24] Wheeler *et al*.[25] analyzed 49 patients who were initially treated with radiotherapy. After local recurrence of prostate cancer, a statistically significant shift to higher grades was seen. The only predicting factor for dedifferentiation was time since diagnosis in the multiple logistic regression analysis. In these studies dedifferentiation could only be studied in a very select group of patients with poor tumor characteristics. Only few men undergo a repeat TURP, and they probably have worse tumor characteristics than men sufficiently treated by a single TURP and similarly for the patients who had recurrence after radiotherapy (3.9%) in the study of Wheeler *et al*.

Tumors in patients choosing watchful waiting instead of curative treatment might be more representative of tumors found in screened populations. Adolfsson and Tribukait[26] studied cytological differentiation in 78 patients with at least 2 fine needle aspiration biopsies taken at an interval of 2 years more. Progression to less differentiated tumors was seen in 18 patients (23%). Johansson *et al*.[5] reported dedifferentiation in 17% of 178 prostate cancer patients with localized disease managed by watchful waiting who underwent repeat fine needle biopsy. Epstein *et al*.[7] reported about patients who were managed by watchful waiting, selected according to the Epstein criteria[27] for insignificant cancer, implying an initial Gleason score less than 7. The protocol indicated yearly prostate biopsy. Seventy patients underwent at least two subsequent biopsies, of whom only 9 (13%) showed an increase in Gleason score from less than 7 to 7 or more. But in only 1 case the increase in Gleason score was observed in a repeat biopsy taken after an interval of more than 24 months. The authors conclude that the higher score might be the result of sampling a higher-grade component initially not sampled. This could also explain the findings by Khan *et al*. who observed progression in biopsies taken within 2 years after diagnosis, but not in the third biopsy taken 3 years after diagnosis.[28]

Our results, based on 2,204 tumors diagnosed in the ERSPC-Rotterdam population-based trial with more than 40,000 participants, suggest that prostatic tumors dedifferentiate during the screen-detectable preclinical phase. In principle, screening and early treatment might be able to prevent some tumors to dedifferentiate to higher Gleason scores. Unfortunately we have not yet been able to verify this directly in our data: in July 2002, after a mean follow-up of 5 years, we found high-grade (Gleason score $>$ 7) tumors in 101 patients in each arm of the trial. This may be disappointing, but not surprising considering that screening with PSA may advance diagnosis with 10 years on average. Given the prognostic value of the Gleason score, our results indicate a potential of screening with PSA to reduce prostate cancer mortality. Final proof of the latter point will of course require more follow-up than 5 years to show up.[29]

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