

Prostate Carcinoma Risk Subsequent to Diagnosis of Benign Prostatic Hyperplasia

A Population-Based Cohort Study in Sweden

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BACKGROUND. Pathologically, benign prostatic hyperplasia (BPH) is not considered a precursor for prostate carcinoma. However, because the two conditions share not only a similar hormonal environment within the prostate but also several common risk factors, it is possible that men with BPH may be at increased risk of prostate carcinoma due to these shared factors.

METHODS. To elucidate this further, the authors used Swedish nationwide population-based record-linkage data to assess prostate carcinoma risk up to 26 years after the diagnosis of BPH among 86,626 men.

RESULTS. Overall, relative to the general population, patients with BPH experienced little, if any, excess risk of prostate carcinoma (2% excess incidence after 10 years of follow-up). However, patients with BPH with and without surgical intervention experienced different prostate carcinoma risk patterns. Those undergoing transvesicular adenectomy had a significant 22% lower incidence and a 23% lower mortality after the first 5 years of follow-up and those undergoing transurethral resection had a significant 10% higher incidence but a 17% lower mortality. In contrast, after the first 5 years, patients with BPH who did not receive surgical intervention experienced significant excesses of both prostate carcinoma incidence (18%) and mortality (77%).

CONCLUSIONS. The differences in prostate carcinoma incidence and mortality by BPH treatment type suggest that factors related to treatment or health reasons underlying the selection of treatment influence subsequent prostate carcinoma risk. Further studies are needed to confirm the minimal excess risk of prostate carcinoma among BPH patients overall and the possible impact of BPH treatment methods on subsequent prostate carcinoma risk. *Cancer* 2003;98:1727-34.

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KEYWORDS: prostate carcinoma, benign prostatic hyperplasia, Sweden, cohort, transurethral resection, transvesical adenectomy, epidemiology.

Benign prostatic hyperplasia (BPH) and prostate carcinoma, two common urologic conditions among elderly men, share not only a similar hormonal milieu within the prostate, but also several epidemiologic and clinical factors. Both conditions increase with advancing age, both require androgens for growth and development, and both respond to antiandrogenic therapy.¹ Greater than 80% of men with prostate carcinoma also have BPH,² and BPH and prostate carcinoma share such putative risk factors as insulin-like growth factors, insulin, and obesity.³⁻⁹ Despite these commonalities, based on histologic evidence and anatomic locations, BPH is currently not considered a precursor lesion for prostate carcinoma.¹⁰ Nevertheless, because of the similarities in risk factors and hormonal environment,

it has been suggested that BPH may predispose to prostate carcinoma or that the two conditions may share one or more etiologic pathways.¹

Previous cohort studies evaluating the relation between BPH and prostate carcinoma have found mixed results,¹¹⁻¹³ but samples were generally small and not population based. To evaluate further the risk of prostate carcinoma after BPH in Sweden, where 8322 hospital diagnoses of BPH were made in 1983, we used nationwide population-based record-linkage data to evaluate prostate carcinoma incidence and mortality rates in a cohort of 86,626 Swedish men diagnosed with BPH and followed for up to 26 years.

MATERIALS AND METHODS

The Population

The record-linkage data and methods of follow-up used in the current study have been described in detail elsewhere.¹⁴ Since 1964, the Swedish National Board of Health and Welfare has recorded hospital discharges in Sweden in the Inpatient Register (IPR). Each record, corresponding to one in-hospital admission, contains an individually unique national registration number, hospital department, surgical procedures, and up to eight discharge diagnoses.¹⁵ These diagnoses were coded according to the seventh revision of the International Classification of Disease (ICD) through 1968,¹⁶ and according to the eighth revision during the rest of the cohort accrual period. In 1965, the IPR covered 16% of the Swedish population, but it expanded rapidly to 60% in 1969, 75% in 1978, and 85% in 1983. Because nearly all hospital beds in Sweden are in public hospitals and virtually all hospital discharges are reported, the IPR is considered essentially complete in the geographic areas covered by the register. It has been estimated that the overall extent of underreporting is less than 2%.¹⁵ Another validation study that compared medical records of 900 hospitalizations with the IPR showed that the agreement rate on main (5-digit and 3-digit) diagnoses was 83-88%.¹⁷

The Cohort

All patients whose records in the IPR contained a diagnostic code for BPH (Swedish ICD7 610.10 and ICD8 600.09) between 1964 and 1983, and whose national registration numbers were complete and referable to a person alive and residing in Sweden at the time of entry (first hospital diagnosis of BPH in the IPR), were included in the cohort. In addition, surgical codes and procedure dates for transurethral resection of the prostate (TURP; a procedure in which urethral obstruction is cleared using a resectoscope inserted into the urethra to remove periurethral prostate tis-

sue) and transvesical adenomectomy (TA; open surgery for the removal of the entire inner core of the prostate, leaving only peripheral zone tissue) were used to identify patients with BPH who received surgical treatment for their condition.

A total of 86,626 patients with a discharge diagnosis of BPH were included in the study. Based on surgical procedure codes, these patients were classified into 1 of 4 mutually exclusive subcohorts based on surgical treatment for BPH: 24,595 (28.4%) had no surgery, 41,100 (47.4%) had TURP, 20,016 (23.1%) had TA, and 915 (1.1%) had both TURP and TA for BPH. Although all subjects were followed for prostate carcinoma mortality, subjects with prevalent prostate tumors at entry ($n = 542$ in the nonsurgical, 583 in the TURP, 124 in the TA, and 8 in the TURP and TA subcohorts) were excluded from the incidence follow-up. Furthermore, prostate carcinomas that were diagnosed incidentally at autopsy were not counted as cases in the incidence analysis. Because there were too few subjects to obtain reliable estimates of prostate carcinoma incidence or mortality, the 915 patients who received TURP and TA were excluded from individual subcohort analyses, but were retained in overall analyses of all BPH patients combined.

Follow-Up

Incident cancer cases diagnosed between 1964 and 1989 in the subcohorts were identified by record linkage of the IPR data to the Swedish Cancer Registry based on national registration numbers. The nationwide cancer registry was established in 1958. By law, all cancer diagnoses must be reported to the registry by both clinicians and pathologists at the time of diagnosis. As a result, greater than 98% of all diagnosed malignant neoplasms in Sweden are ascertained.¹⁸ Data concerning stage and grade of diagnosed malignancies are not recorded.

Similarly, deaths in the subcohorts were ascertained through record linkage to the Swedish National Death Register. In Sweden, a physician must certify all deaths and the certificates are forwarded to Statistics Sweden via the population registrars.¹⁹ Underlying causes of death were coded in accordance with the ICD7 (1964-1968), ICD8 (1969-1986), and ICD9 (1987-1989).²⁰

Person-years at risk in the subcohorts were calculated from the admission date for the hospital visit during which BPH was first diagnosed to the date of first prostate carcinoma (incidence analysis), date of prostate carcinoma death (mortality analysis), date of death from other causes, date of emigration, or end of the observation period (December 31, 1989), whichever occurred first after BPH.

TABLE 1
Characteristics of Patients Diagnosed with Benign Prostatic Hyperplasia in Sweden, 1964–1983

| Characteristics | All patients with BPH | BPH without surgery | BPH with TURP | BPH with TA |
|--|-----------------------|---------------------|---------------|-------------|
| No. of patients | 86,626 | 24,595 | 41,100 | 20,016 |
| Total person-yrs | 641,893 | 137,564 | 307,481 | 187,171 |
| No. of subsequent prostate carcinomas | 4875 | 2260 | 1748 | 824 |
| No. of prostate carcinoma deaths | 2300 | 1209 | 635 | 427 |
| Average no. of yrs of follow-up | 7.4 | 5.6 | 7.5 | 9.4 |
| Average age at entry (BPH diagnosis) (yrs) | 71.4 | 74.3 | 70.2 | 70.5 |
| Average calendar yr of BPH diagnosis | 1978 | 1976 | 1980 | 1976 |
| Average age at subsequent prostate carcinoma diagnosis (yrs) | 76.7 | 76.1 | 76.7 | 78.0 |
| Average calendar yr of subsequent prostate carcinoma diagnosis | 1981 | 1978 | 1984 | 1982 |
| Average age at prostate carcinoma death (yrs) | 79.6 | 80.2 | 78.9 | 79.9 |
| Average calendar yr of prostate carcinoma death | 1982 | 1980 | 1984 | 1982 |

BPH: benign prostatic hyperplasia; TURP: transurethral resection of the prostate; TA: transvesical adenectomy.

Statistical Analysis

The expected numbers of prostate carcinoma cases and deaths were calculated by multiplying the number of person-years by the age-specific cancer incidence and cause-specific mortality rates in Sweden for each 5-year age group and calendar year of observation. In calculating the expected numbers of prostate carcinoma cases, we excluded prevalent prostate carcinoma cases from the general Swedish population to match the similar exclusion in the study cohort. Because the general population is large and prostate carcinoma incidence and mortality are relatively low, the observed numbers of events (incident prostate carcinomas or prostate carcinoma deaths) can be assumed to follow a Poisson distribution, with a mean value equal to the expected number derived from the population. Standardized incidence rates (SIRs) and standardized mortality rates (SMRs), calculated as the ratio of the observed to the expected numbers of events, and their 95% confidence intervals (95% CIs) were computed to quantify the associations between BPH and prostate carcinoma.²¹

RESULTS

During the 26-year follow-up period (641,893 person-years), we observed 4875 incident primary prostate carcinomas overall, including 2260 among the patients with BPH who did not receive surgery, 1748 among the patients with BPH who received TURP, and 824 among the patients with BPH who received TA (Table 1). In addition, we observed 2300 total prostate carcinoma deaths. BPH patients treated with TURP and TA were younger at BPH diagnosis than those in the nonsurgical subcohort (70.2 years and 70.5 years vs. 74.3 years, respectively). Among patients who developed subsequent prostate carcinoma, the mean in-

terval between BPH diagnosis and prostate carcinoma diagnosis was longer among men in the TURP and TA subcohorts (6.5 years and 7.5 years) versus men in the nonsurgical subcohort (1.8 years).

Table 2 shows the incidence of prostate carcinoma in the total BPH cohort, and then separately for each subcohort. Excluding the first 5 years of follow-up, during which increased surveillance, selection or protopathic bias due to previously undiagnosed prostate carcinoma concomitant with BPH, or misdiagnosis of prostate carcinoma as BPH would be expected to elevate SIRs, we observed no excess incidence in the total cohort for the entire follow-up period (SIR = 0.99) or for any individual time periods. However, the SIRs for patients with BPH who did receive prostate surgery were slightly but significantly elevated after excluding the first 5 years of follow-up (SIR = 1.18; 95% CI, 1.07–1.30) and were nonsignificantly elevated for Years 11–26 (SIR = 1.09). In contrast, early in the follow-up period, the TURP subcohort experienced significantly reduced SIRs, which gradually increased and became significantly elevated. After excluding the first 5 follow-up years, the TURP subcohort showed a slight but significant overall excess prostate carcinoma incidence (SIR = 1.10; 95% CI, 1.03–1.17) and after excluding the first 10 years, the SIR was 1.21. Similarly, in the beginning of the follow-up period, the TA subcohort experienced significantly reduced SIRs that gravitated toward the null with follow-up. However, in contrast to the TURP subcohort, the TA subcohort maintained a reduced incidence after excluding the first 5 (SIR = 0.78; 95% CI, 0.72–0.85) and 10 years (SIR = 0.88; 95% CI, 0.77–1.00).

Because BPH management and surgical practice changed in Sweden during the 1970s and 1980s, with TURP gradually replacing TA and over time removing

TABLE 2
Standardized Incidence Ratios and 95% Confidence Intervals for Prostate Carcinoma among Patients Diagnosed with Benign Prostatic Hyperplasia in Sweden, 1964–1983

| Yrs of follow-up | All patients with BPH (n = 85,369) | | | BPH without surgery (n = 24,053) | | | BPH with TURP (n = 40,517) | | | BPH with TA (n = 19,892) | | |
|------------------|------------------------------------|--------|------------------|----------------------------------|-------|--------------------|----------------------------|-------|------------------|--------------------------|-------|------------------|
| | Obs | Exp | SIR (95% CI) | Obs | Exp | SIR (95% CI) | Obs | Exp | SIR (95% CI) | Obs | Exp | SIR (95% CI) |
| 1 | 1540 | 367.7 | 4.19 (3.98–4.40) | 1226 | 110.3 | 11.11 (10.5–11.75) | 253 | 171.0 | 1.48 (1.30–1.67) | 58 | 83.0 | 0.70 (0.53–0.90) |
| 2 | 442 | 372.2 | 1.19 (1.08–1.30) | 251 | 96.8 | 2.59 (2.28–2.93) | 144 | 181.5 | 0.79 (0.67–0.93) | 46 | 90.2 | 0.51 (0.37–0.68) |
| 3 | 360 | 365.3 | 0.99 (0.89–1.09) | 154 | 85.2 | 1.81 (1.53–2.12) | 139 | 183.8 | 0.76 (0.64–0.89) | 67 | 92.3 | 0.73 (0.56–0.92) |
| 4 | 305 | 357.4 | 0.85 (0.76–0.95) | 118 | 75.5 | 1.56 (1.29–1.87) | 128 | 184.2 | 0.69 (0.58–0.83) | 55 | 93.7 | 0.59 (0.44–0.76) |
| 5–6 | 692 | 684.5 | 1.01 (0.94–1.09) | 184 | 128.3 | 1.43 (1.23–1.66) | 364 | 360.7 | 1.01 (0.91–1.12) | 135 | 187.4 | 0.72 (0.60–0.85) |
| 7–8 | 545 | 563.0 | 0.97 (0.89–1.05) | 115 | 96.5 | 1.19 (0.98–1.43) | 307 | 285.2 | 1.08 (0.96–1.20) | 114 | 173.2 | 0.66 (0.54–0.79) |
| 9–10 | 372 | 389.2 | 0.96 (0.86–1.06) | 77 | 69.3 | 1.11 (0.88–1.39) | 188 | 170.9 | 1.10 (0.95–1.27) | 104 | 142.1 | 0.73 (0.60–0.89) |
| 11–15 | 484 | 475.6 | 1.02 (0.93–1.11) | 100 | 92.4 | 1.08 (0.88–1.32) | 184 | 158.8 | 1.16 (1.00–1.34) | 188 | 212.4 | 0.89 (0.76–1.02) |
| 16–26 | 135 | 130.3 | 1.04 (0.87–1.23) | 35 | 31.8 | 1.10 (0.77–1.53) | 41 | 27.9 | 1.47 (1.06–2.00) | 57 | 66.0 | 0.86 (0.65–1.12) |
| 6–26 | 1884 | 1894.6 | 0.99 (0.95–1.04) | 414 | 350.7 | 1.18 (1.07–1.30) | 903 | 821.2 | 1.10 (1.03–1.17) | 536 | 687.1 | 0.78 (0.72–0.85) |
| 11–26 | 619 | 605.9 | 1.02 (0.94–1.11) | 135 | 124.2 | 1.09 (0.91–1.29) | 225 | 186.7 | 1.21 (1.05–1.37) | 245 | 278.4 | 0.88 (0.77–1.00) |

BPH: benign prostatic hyperplasia; TURP: transurethral resection of the prostate; TA: transvesical adenectomy; Obs: observed; Exp: expected; SIR: standardized incidence ratio; 95% CI: 95% confidence interval.

TABLE 3
Standardized Incidence Ratios and 95% Confidence Intervals for Prostate Carcinoma among Patients Diagnosed with Benign Prostatic Hyperplasia in Sweden, by Year of Benign Prostatic Hyperplasia Diagnosis

| Yr of BPH diagnosis | Yrs of follow-up | All patients with BPH | | | BPH without surgery | | | BPH with TURP | | | BPH with TA | | |
|---------------------|------------------|-----------------------|-----------------|-----------------|---------------------|---------------------|---------------------|---------------|-----------------|-----------------|-------------|------------------|------------------|
| | | Obs | Exp | SIR (95% CI) | Obs | Exp | SIR (95% CI) | Obs | Exp | SIR (95% CI) | Obs | Exp | SIR (95% CI) |
| 1964–1969 | | (n = 6686) | | | (n = 3024) | | | (n = 838) | | | (n = 2701) | | |
| | 1 | 144 | 24.4 | 5.9 (4.98–6.96) | 129 | 11.7 | 11.04 (9.22–13.12) | 6 | 2.8 | 2.1 (0.79–4.71) | 8 | 9.6 | 0.83 (0.36–1.64) |
| | 2–4 | 110 | 73.2 | 1.5 (1.24–1.81) | 90 | 30.2 | 2.98 (2.40–3.67) | 5 | 9.2 | 0.5 (0.18–1.27) | 15 | 32.6 | 0.46 (0.26–0.76) |
| | 5–10 | 137 | 125.2 | 1.0 (0.92–1.29) | 72 | 41.7 | 1.73 (1.35–2.17) | 21 | 17.2 | 1.2 (0.76–1.87) | 42 | 63.2 | 0.66 (0.48–0.90) |
| 1970–1974 | 11–26 | 145 | 136.9 | 1.0 (0.89–1.25) | 46 | 37.7 | 1.22 (0.89–1.63) | 32 | 21.9 | 1.4 (1.00–2.06) | 63 | 72.0 | 0.88 (0.67–1.12) |
| | | (n = 16,283) | | | (n = 6335) | | | (n = 3774) | | | (n = 5906) | | |
| | 1 | 326 | 67.3 | 4.8 (4.33–5.4) | 289 | 29.1 | 9.93 (8.82–11.15) | 19 | 13.8 | 1.3 (0.83–2.15) | 18 | 23.5 | 0.77 (0.45–1.21) |
| | 2–4 | 271 | 189.1 | 1.4 (1.27–1.61) | 184 | 66.7 | 2.76 (2.37–3.19) | 34 | 42.8 | 0.7 (0.55–1.11) | 53 | 76.3 | 0.69 (0.52–0.91) |
| 1975–1979 | 5–10 | 296 | 312.3 | 0.9 (0.84–1.06) | 101 | 80.6 | 1.25 (1.02–1.52) | 89 | 79.6 | 1.1 (0.90–1.38) | 98 | 144.9 | 0.68 (0.55–0.82) |
| | 11–26 | 269 | 267.9 | 1.0 (0.89–1.13) | 59 | 57.0 | 1.04 (0.79–1.34) | 90 | 72.1 | 1.2 (1.00–1.54) | 112 | 131.1 | 0.85 (0.70–1.03) |
| | | (n = 29,113) | | | (n = 8053) | | | (n = 13,421) | | | (n = 7278) | | |
| | 1 | 499 | 122.1 | 4.0 (3.74–4.46) | 410 | 36.4 | 11.26 (10.20–12.41) | 70 | 53.9 | 1.3 (1.01–1.64) | 18 | 30.5 | 0.59 (0.35–0.93) |
| 1980–1984 | 2–4 | 364 | 364.7 | 1.0 (0.90–1.11) | 148 | 84.7 | 1.75 (1.48–2.05) | 152 | 172.6 | 0.8 (0.75–1.03) | 61 | 102.5 | 0.60 (0.46–0.76) |
| | 5–10 | 626 | 641.6 | 0.9 (0.90–1.06) | 135 | 106.1 | 1.27 (1.07–1.51) | 338 | 321.3 | 1.0 (0.94–1.17) | 143 | 204.7 | 0.70 (0.59–0.82) |
| | 11–26 | 205 | 201.0 | 1.0 (0.88–1.17) | 30 | 29.5 | 1.02 (0.69–1.45) | 103 | 92.7 | 1.1 (0.91–1.35) | 70 | 75.3 | 0.93 (0.72–1.17) |
| | | (n = 33,287) | | | (n = 6636) | | | (n = 22,484) | | | (n = 4007) | | |
| 1 | 571 | 153.9 | 3.7 (3.41–4.03) | 398 | 33.1 | 12.01 (10.86–13.25) | 158 | 100.6 | 1.5 (1.34–1.84) | 14 | 19.4 | 0.72 (0.39–1.21) | |
| 2–4 | 362 | 468.0 | 0.7 (0.70–0.86) | 101 | 75.9 | 1.33 (1.08–1.62) | 220 | 324.9 | 0.6 (0.59–0.77) | 39 | 64.7 | 0.60 (0.43–0.82) | |
| 5–10 | 550 | 557.6 | 0.9 (0.91–1.07) | 68 | 65.7 | 1.04 (0.80–1.31) | 411 | 398.7 | 1.0 (0.93–1.14) | 70 | 89.9 | 0.78 (0.61–0.98) | |

BPH: benign prostatic hyperplasia; TURP: transurethral resection of the prostate; TA: transvesical adenectomy; Obs: observed; Exp: expected; SIR: standardized incidence ratio; 95% CI: 95% confidence interval.

increasing amounts of prostate tissue, we evaluated the incidence results after stratifying by calendar year of BPH diagnosis (Table 3). In the overall BPH cohort, prostate carcinoma incidence rates in later years of follow-up (years 5–10 and years 11–26) were nonsignificantly different from unity for all calendar year groups. Among men in the nonsurgical subcohort, those whose BPH was diagnosed in earlier calendar years had higher SIRs relative to men whose BPH was

diagnosed in later calendar years (5–10-year latency SIRs in 1964–1969 and 1980–1984 were 1.73 and 1.04, respectively). Similar reductions in SIRs with later calendar year of BPH diagnosis were observed for patients treated with TURP, whereas no appreciable differences were noted for the TA subcohort.

For virtually all follow-up years, the BPH cohort as a whole experienced prostate carcinoma mortality rates similar to those of the general population (Table

TABLE 4
Standardized Mortality Ratios and 95% Confidence Intervals for Prostate Carcinoma among Patients Diagnosed with Benign Prostatic Hyperplasia in Sweden, 1964–1983

| Yrs of follow-up | All patients with BPH (n = 86,626) | | | BPH without surgery (n = 24,595) | | | BPH with TURP (n = 41,100) | | | BPH with TA (n = 20,016) | | |
|------------------|------------------------------------|--------|------------------|----------------------------------|-------|------------------|----------------------------|-------|------------------|--------------------------|-------|------------------|
| | Obs | Exp | SMR (95% CI) | Obs | Exp | SMR (95% CI) | Obs | Exp | SMR (95% CI) | Obs | Exp | SMR (95% CI) |
| 1 | 234 | 191.4 | 1.22 (1.07–1.39) | 202 | 69.6 | 2.90 (2.52–3.33) | 16 | 81.2 | 0.20 (0.11–0.32) | 15 | 39.1 | 0.38 (0.21–0.63) |
| 2 | 251 | 194.7 | 1.29 (1.13–1.46) | 181 | 62.3 | 2.91 (2.50–3.36) | 52 | 86.9 | 0.60 (0.45–0.78) | 17 | 43.7 | 0.39 (0.23–0.62) |
| 3 | 267 | 190.8 | 1.40 (1.24–1.58) | 169 | 55.0 | 3.07 (2.63–3.57) | 66 | 88.1 | 0.75 (0.58–0.95) | 32 | 45.7 | 0.70 (0.48–0.99) |
| 4 | 240 | 186.7 | 1.29 (1.13–1.46) | 133 | 48.7 | 2.73 (2.29–3.24) | 80 | 88.8 | 0.90 (0.71–1.12) | 26 | 47.2 | 0.55 (0.36–0.81) |
| 5–6 | 420 | 360.6 | 1.16 (1.06–1.28) | 207 | 82.4 | 2.51 (2.18–2.88) | 139 | 177.2 | 0.78 (0.66–0.93) | 70 | 96.9 | 0.72 (0.56–0.91) |
| 7–8 | 312 | 302.8 | 1.03 (0.92–1.15) | 116 | 62.0 | 1.87 (1.55–2.25) | 118 | 143.9 | 0.82 (0.68–0.98) | 73 | 92.8 | 0.79 (0.62–0.99) |
| 9–10 | 206 | 216.9 | 0.95 (0.82–1.09) | 75 | 45.0 | 1.67 (1.31–2.09) | 65 | 89.4 | 0.73 (0.56–0.93) | 61 | 78.8 | 0.77 (0.59–0.99) |
| 11–15 | 280 | 280.1 | 1.00 (0.89–1.12) | 101 | 60.3 | 1.68 (1.36–2.04) | 78 | 88.0 | 0.89 (0.70–1.11) | 93 | 125.0 | 0.74 (0.60–0.91) |
| 16–26 | 90 | 85.5 | 1.05 (0.85–1.29) | 25 | 22.1 | 1.13 (0.73–1.67) | 21 | 17.2 | 1.22 (0.75–1.86) | 40 | 43.5 | 0.92 (0.66–1.25) |
| 6–26 | 1081 | 1063.2 | 1.02 (0.96–1.08) | 405 | 228.2 | 1.77 (1.61–1.96) | 353 | 426.7 | 0.83 (0.74–0.92) | 299 | 388.8 | 0.77 (0.68–0.86) |
| 11–26 | 370 | 365.7 | 1.01 (0.91–1.12) | 126 | 82.4 | 1.53 (1.27–1.82) | 99 | 105.2 | 0.94 (0.76–1.15) | 133 | 168.5 | 0.79 (0.66–0.94) |

BPH: benign prostatic hyperplasia; TURP: transurethral resection of the prostate; TA: transvesical adenectomy; Obs: observed; Exp: expected; SMR: standardized mortality ratio; 95% CI: 95% confidence interval.

TABLE 5
Overall Standardized Mortality Ratios from Comorbidities

| Characteristics | All patients with BPH (n = 86,626) | BPH without surgery (n = 24,595) | BPH with TURP (n = 41,100) | BPH with TA (n = 20,016) |
|--|------------------------------------|----------------------------------|----------------------------|--------------------------|
| | SMR (95% CI) | SMR (95% CI) | SMR (95% CI) | SMR (95% CI) |
| Diabetes mellitus (ICD7: 260; ICD8-9: 250) | 1.30 (1.21–1.40) | 2.33 (2.08–2.60) | 1.08 (0.95–1.22) | 0.80 (0.67–0.95) |
| Cardiovascular disease (ICD7: 400–468; ICD8: 390–458; ICD9: 390–459) | 1.10 (1.09–1.11) | 1.60 (1.57–1.63) | 0.98 (0.96–1.00) | 0.87 (0.85–0.89) |
| Respiratory disease (ICD7: 470–527; ICD8-9: 460–519) | 1.17 (1.13–1.20) | 1.85 (1.77–1.94) | 1.02 (0.97–1.06) | 0.83 (0.77–0.88) |

BPH: benign prostatic hyperplasia; TURP: transurethral resection of the prostate; TA: transvesical adenectomy; SMR: standardized mortality ratio; 95% CI: 95% confidence interval; ICD: International Classification of Diseases.

4). However, the nonsurgical subcohort experienced a significant threefold excess prostate carcinoma mortality early in the follow-up period, followed by a decline to an SMR of 1.53 (95% CI, 1.27–1.82) after excluding the first 10 years of follow-up. In contrast, both the TA and the TURP subcohorts experienced significantly lower prostate carcinoma mortality rates early in the follow-up period. After excluding the first 10 years of follow-up, the mortality reduction in the TURP subcohort became nonsignificant (SMR = 0.94; 95% CI, 0.76–1.15), whereas the SMR for the TA subcohort remained significantly decreased (SMR = 0.79; 95% CI, 0.66–0.94).

To investigate whether choice of treatment for BPH may have been related to health status, we calculated the overall age and calendar year SMRs from cardiovascular disease, diabetes, and respiratory disease for each subcohort. Overall, patients with BPH had significantly elevated mortality from other causes

relative to the general population (Table 5). However, although men in the nonsurgical subcohort experienced significantly elevated mortality from these comorbidities, men in the TURP subcohort experienced no excess mortality from these conditions and men in the TA subcohort experienced a significantly lower mortality.

DISCUSSION

In this large population-based cohort study in Sweden, we found that after 26 years of follow-up, men with a hospital discharge diagnosis of BPH experienced little, if any, excess risk of prostate carcinoma compared with the general population (1% lower incidence and 2% excess mortality after the first 5 years). However, BPH patients with and without surgical intervention experienced different risk patterns. Those undergoing the TA procedure had a 22% reduction in prostate carcinoma incidence and a 23% reduction in

mortality after the first 5 years, those undergoing TURP experienced a 10% excess incidence but a 17% reduction in mortality, and those without surgical intervention experienced an 18% excess incidence and a 77% excess mortality. These differences across subcohorts suggest that factors related to treatment or selection of treatment may have impacted the subsequent risk of prostate carcinoma among patients with BPH.

It is likely that differences in the incidence and mortality experiences in the subcohorts may be related to a number of factors, including the 1) selection of healthier patients with BPH for certain surgical treatments, 2) removal of prostate tissue among patients with BPH undergoing surgery, 3) increased surveillance of prostate carcinoma among certain groups of patients with BPH, and perhaps 4) differential exclusion from incidence analyses of prevalent prostate carcinomas identified at the time of BPH diagnosis.

Men undergoing the TA procedure (open prostatic surgery) had lower prostate carcinoma incidence and mortality from prostate carcinoma relative to men undergoing TURP. This may be due in part to selection of healthier men for the open procedure, as suggested by the significantly lower mortality from other comorbidities (including cardiovascular disease, diabetes, and respiratory disease) than those undergoing TURP. Indeed, patients with BPH undergoing any prostatic surgery were generally healthier than those without surgical intervention, as suggested by their lower age at entry and lower mortality from other comorbidities. This is also supported by the observation that the index hospital discharge BPH diagnosis was a secondary diagnosis for 47% of the men in the nonsurgical subcohort, versus 11% and 12%, respectively, for men in the TA and TURP subcohorts, indicating that men in the nonsurgical subcohort were more likely to have gained hospital admission on the index date for other illnesses. Because a variety of factors relating to overall health, including diet, physical activity, and obesity, have been linked to increased prostate carcinoma risk,²²⁻²⁵ it is possible that underlying treatment selection factors related to better health may have contributed to the observed differences in prostate carcinoma incidence and mortality across subcohorts.

The observation that patients with BPH undergoing TA had substantially lower prostate carcinoma incidence and mortality throughout most of the follow-up period also may relate to the finding that at the time of the study, TURPs were usually performed by specialists whereas TAs were more often performed by general surgeons. If prostate carcinoma was suspected (presumably on the basis of a digital rectal examina-

tion), a physician would refer the patient to a specialist. Otherwise, the patient would be referred to a general surgeon. Consequently, patients with BPH undergoing TA (most often performed by a general surgeon) were likely a select group much less likely to have prostate carcinoma, whereas those in the TURP subcohort likely included more patients with BPH who had access to a specialist and in whom the referring physician either suspected or could not exclude prostate carcinoma. That TURP-treated patients with BPH experienced a delayed but significantly elevated prostate carcinoma incidence without significantly elevated prostate carcinoma mortality supports the suggestion that BPH surgery candidates in whom prostate carcinoma was suspected were given TURP rather than TA. This is reflected in the time trends of BPH diagnosis as well. Prostate carcinoma SIRs declined with calendar year of diagnosis in the TA subcohort as TURP replaced TA over time (TURP comprised 22.9% of BPH surgeries in 1964-1969 vs. 84.4% in 1980-1984).

The lower prostate carcinoma mortality observed among patients with BPH undergoing either TURP or TA may have resulted from the possibility that these surgical procedures may have reduced the amount of prostate tissue at risk for cancer, thereby reducing the probability of development of clinically significant prostate carcinoma among surgically treated patients with BPH. In Sweden, the TA procedure removes the central core of the prostate, leaving intact the peripheral zone, in which the majority of tumors occur. In contrast, although the TURP procedure generally involves removal of small amounts periurethral tissue (transition zone, in which few tumors occur), deeper resections can remove parts of the central zone and even the peripheral zone. Indeed, as the TURP procedure improved, it involved removal of increasing amounts of prostate tissue, likely contributing to the reductions in incidence observed in the TURP subcohort over calendar time.

Increased surveillance also may have contributed to the slight excess prostate carcinoma incidence among nonsurgical patients with BPH. This is particularly evident in the high SIRs noted in the first few years of follow-up. However, these SIRs decreased with increasing duration of follow-up and were no longer statistically significant by the end of the study, suggesting that much of the early excess in incidence among the nonsurgically treated patients with BPH was likely because of increased surveillance. Furthermore, although increased detection does not explain the excess prostate carcinoma mortality observed among these patients (77% excluding the first 5 follow-up years), the SMR decreased to a nonsignificant

13% excess by the last 10 years of follow-up, suggesting that the excess risk of death due to prostate carcinoma among these patients with BPH is minimal. The reasons for and the public health significance of the small excess prostate carcinoma incidence and mortality among nonsurgically treated patients with BPH are unclear. Because the use of nonsurgical BPH treatment is an increasingly common practice in Sweden and other Western countries,^{26,27} further studies should be conducted to confirm this excess risk among nonsurgical patients with BPH.

In addition, the more marked SIR elevations in the nonsurgical versus the surgical subcohorts during the early follow-up years may be due, at least in part, to the combination of the exclusion of diagnosed prevalent prostate carcinomas from the incidence analyses and the availability of surgically removed prostate tissue for histologic evaluation and diagnosis in the two surgical subcohorts but not the nonsurgical subcohort. As such, the nonsurgically treated subcohort would include a greater proportion of undiagnosed prevalent prostate carcinomas, thereby inflating the SIRs relative to the surgically treated subcohorts.

The possibility that the slight excess incidence observed among patients with BPH undergoing TURP or nonsurgical intervention may be real (i.e., have biologic causes) cannot be ruled out completely. Although BPH is not considered a precursor lesion for prostate carcinoma, because the two conditions share not only a similar hormonal environment within the prostate but also many common risk factors, it is possible that patients with BPH may have a higher risk of prostate carcinoma due merely to these shared factors. The results of the current study suggest that if this is so, any potential excess risk of prostate carcinoma among patients with BPH is likely to be small.

The current study has several unique strengths. Possible bias due to selection of patients with BPH into the overall cohort is minimal because of the population-based nature of the IPR. In addition, the completeness of cancer reporting in the current study, attributable to the comprehensive records system in Sweden, further minimizes possible biases due to selection and nonresponse. The accuracy of cancer diagnoses in Sweden is also high, due to the high proportion of histologic confirmation (> 90%). Furthermore, the large sample size and long duration of follow-up in the current study provide sufficient statistical power and permit evaluation of risk by type of BPH surgery. In addition, the population rates used to calculate the expected numbers of prostate carcinomas account for prostate carcinomas prevalent in the population. Therefore, the potential bias associated with excluding prevalent prostate carcinomas from

the BPH cohort, but not the general Swedish population, is minimized. Finally, because the study period (1964–1989) predates widespread prostate-specific antigen-based prostate carcinoma screening in Sweden, and because latent, clinically unimportant prostate tumors that may only be detected through screening are extremely common among older men, the current study focuses on the risk of clinically important prostate carcinoma after a BPH diagnosis.

Perhaps due, in part, to the strengths noted earlier, the results of this large, population-based study of prostate carcinoma after BPH differ somewhat from those of three smaller previous investigations that included only men with surgically treated BPH. In contrast to the slight excess incidence observed among TURP-treated patients in the current investigation, 1 previous study found no excess prostate carcinoma incidence in a cohort of 838 patients with BPH undergoing TURP.¹¹ In addition, the slightly reduced prostate carcinoma mortality observed among each of the groups of surgically treated patients with BPH in the current study contrasts with results from the other two studies, which show a nonsignificantly elevated mortality in a cohort of 4853 men surgically treated for BPH¹³ and a markedly elevated mortality in a cohort of 296 patients with BPH.¹² Furthermore, to our knowledge, the current study is the first to reflect the prostate carcinoma experience of both surgically and nonsurgically treated patients with BPH, and shows no overall excess incidence in the overall cohort of patients with BPH, irrespective of surgery.

Limitations of this study should be noted. Because we do not have information concerning the clinical stage and histologic grade of prostate carcinomas in this cohort, we cannot determine whether the prostate tumors were detected because of increased surveillance and therefore of lower stage or grade among these patients with BPH than tumors diagnosed in the general Swedish population. Thus, we are unable to assess the extent of surveillance bias in the current study. However, exclusion of the prostate carcinoma cases diagnosed during the first 5 or 10 years of follow-up minimizes the influence of surveillance bias on observed incidence. Because both BPH and prostate carcinoma are age-related conditions, it is possible that age standardization using 5-year intervals may have underestimated the expected numbers of events, thereby biasing toward a positive association. Despite this, however, we observed no overall excess in incidence or mortality among patients with BPH. In addition, although the study is population based and the IPR captures most diagnoses of BPH in Sweden, we are not able to include patients with BPH who have never been either hospitalized or included in the IPR.

However, because of the wide availability of health care in Sweden, the spectrum of BPH among cases not included in the study is undoubtedly milder than that of those who were included. Furthermore, we had no data on factors other than age and calendar year to control for potential confounding.

The results of this large, population-based cohort study in Sweden suggest that as a whole, men diagnosed with BPH experience little, if any, excess prostate carcinoma incidence or mortality. However, the different incidence and mortality patterns observed for surgically and nonsurgically treated patients with BPH suggest that factors related to treatment or the underlying reasons for choice of treatment may influence prostate carcinoma risk. Given the recent shift toward nonsurgical interventions for BPH management in most Western countries, further studies with specific information on clinical stage and histologic grade are needed to confirm both the minimal excess risk of prostate carcinoma among patients with BPH and whether BPH treatment methods have an impact on subsequent prostate carcinoma risk.

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