ORIGINAL ARTICLE

Shift Work and Prostate Cancer Incidence in Industrial Workers

A Historical Cohort Study in a German Chemical Company

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SUMMARY

Background: There is inconsistent evidence for a possible carcinogenic effect of shift work. In particular, little is known about the putative association of shift work with prostate cancer.

Method: We studied a cohort of 27 828 male industrial production workers residing in the German federal state of Rhineland-Palatinate who worked for at least one year in a chemical company in the period 1995–2005. We obtained data on shift work and potential confounders including age, occupational task, and duration of employment from personnel files and from the records of the occupational health service. New cases of cancer in the period 2000–2009 were ascertained from the state cancer registry. Differences in risk between shift workers and daytime workers were analyzed with Cox regression, stratified by stage of cancer, and adjusted for potential confounding effects.

Results: There were 146 new cases of prostate cancer in 12 609 rotating shift workers and 191 in 15 219 daytime workers. The median year of birth was 1960 in the first group and 1959 in the second. The shift workers did not have an elevated hazard ratio for prostate cancer in comparison to the daytime workers (HR = 0.93, 95% confidence interval [CI] 0.73–1.18). Some differences were seen depending on tumor stage. Both groups of workers had a higher incidence of prostate carcinoma than the general population (standardized incidence rate [SIR] = 1.44, 95% CI 1.22–1.70 for daytime workers; SIR = 1.51, 95% CI 1.30–1.74 for shift workers).

Conclusion: In this well-documented, large-scale cohort study, the incidence of prostate cancer among shift workers did not differ from that among daytime workers. In the authors' opinion, further follow-up of this relatively young cohort is required.

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In 2007 the International Agency for Research on Cancer (IARC) classified shift work involving circadian disruption as a probable human carcinogen (1). Most of the evidence for this is based on animal experiment models and only a few reliable epidemiological studies. The cancer best described to date is breast cancer; this has mainly been investigated in female nurses and flight attendants (2, 3).

Shift work can also increase the incidence of prostate cancer, as plausibly described in a review article published in 2012 (4). Mechanistically, it is possible that nocturnal light exposure and disrupted circadian rhythms cause cancer, or that tumor growth is favored by hormonal mediation. Nocturnal light exposure suppresses melatonin secretion in the pineal gland. *In vitro* and *in vivo* experiments have shown that melatonin prevents or inhibits tumor growth, particularly that of prostate cancer, and that there is a dose–effect relationship (1, 5).

The epidemiological evidence on prostate cancer comes from only a few studies involving individual data on shift work (6–8) (Table 1). In studies of flight personnel, duration of employment or number of flight hours was used as a proxy measure (9–11). In one large Scandinavian study, the probability of exposure was estimated using a job exposure matrix (12).

Earlier research of a cohort of 31 143 male production workers in the chemical industry, 45% of whom worked shifts, showed no overall increase in deaths from cancer or individual tumors (13, 14).

This article investigates the incidence of prostate cancer in this cohort and examines earlier findings on overall tumor incidence in more detail (15). The complete scientific report is available online (16).

Methods

Study design, study population

This study is based on a cohort already described in detail by Oberlinner et al. (17) of all male production workers who were employed for at least one year at BASF SE, Ludwigshafen between 1995 and 2005. Information on shift work and potential confounding factors such as age, smoking, professional status, and duration of employment were recorded using personnel files and medical records. BASF SE

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TABLE 1

Review of earlier studies on shift work and on prostate cancer

Main author	Type	Study participants	No. of prostate cancer cases	Recording of chronodisruption	Findings
Conlon (2007) (6)	Case-control study	Prostate cancer patients and control patients in Canada	369 rotating shift workers, 391 daytime workers	Questionnaire: normal shift status	OR = 1.19 (95% CI: 1.00 to 1.42)
Kubo (2006) (7)	Cohort study	14 052 Japanese industrial workers	7 changing shift workers, 3 night shift workers, 21 daytime workers	Questionnaire: longest period of employment	IRR = 2.5 (95% CI: 1.0 to 6.2)
Kubo (2011) (8)	Cohort study	4995 Japanese industrial workers	4 night shift workers, 13 day shift workers	Shift status from database for January 2009	IRR = 1.79 (95% CI: 0.57 to 5.68)
Hammer (2014) (9)	Cohort study	36 816 pilots, 12 288 flight attendants	144 pilots, 17 flight attendants	Duration of employment	SMR = 1.23 (95% CI: 0.98 to 1.53); SMR = 0.75 (95% CI: 0.40 to 1.29)
Pukkala (2002) (10)	Cohort study	10 032 Scandinavian pilots	64	Duration of employment, flight hours	SIR = 1.21 (95% CI: 0.93 to 1.54) Flight hours: $p = 0.12$
Pukkala (2012) (11)	Cohort study	1559 Scandinavian flight attendants	24	Duration of employment	SIR = 1.11 (95% CI: 0.71 to 1.65)
Pukkala (2009) (12)	Ecological study	15 million Scandinavian employees	340 000	Duration of employment from census data	Estimator per occupational group

IRR: Incidence rate ratio; OR: Odds ratio; SMR: Standardized mortality ratio; SIR: Standardized incidence rate; 95% CI: 95% confidence interval; p : p -value

knows whether these individuals are now alive or deceased because former employees receive a company pension.

For this study the cohort was limited to the 12 609 shift workers and 15 219 day workers resident in Rhineland-Palatinate. Incident cancer cases between 2000 and 2009 were identified using the Rhineland-Palatinate Cancer Registry by matching pseudonymized data (18–20). The registry's degree of completeness since 2000 is at over 90% (21). Cancer Registry data specialists checked all potential matches and classified them as good, medium, or poor.

In order to investigate the extent to which health-related behavior depends on shift status, evaluation was broken down by tumor stage T (22). T stage during the observation period is known for 70 to 75% of all registered prostate cancers. Where it is not known, this is usually when a biopsy was performed due to an abnormal prostate-specific antigen (PSA) test at stage T1.

In line with the data protection regulations for comparing cohort studies, which have been approved by the Rhineland-Palatinate State Official for Data Protection (www.datenschutz.rlp.de), pseudonymized epidemiological information on exposure and health was sent to the Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI, Institut für Medizinische Biometrie, Epidemiologie und Informatik) at Mainz University Medical Center for evaluation. All dates and ages were rounded off to the nearest year before the data was sent.

Shift patterns

Two different 12-hour shift patterns are authorized at the Ludwigshafen location. The older pattern (3×12 hours) was used for fifty years; the 4×12 hours patterns was introduced in 1992 and is now used almost exclusively. In the 3×12 hours pattern, a 12-hour day shift from 6 a.m. to 6 p.m. is followed by 24 hours off, a 12-hour night shift, and another 24 hours off. In the 4×12 hours pattern, the second free period lasts 48 hours. Both patterns are forward-rotating and have the same annual working time—1709 hours—and the same number of night shifts. This is achieved using different numbers of free shifts and leave days.

Employment history

Whether individuals worked shifts or daytime hours on the start date of January 1, 1995, or on inclusion in the cohort, was known for all employees. This status was taken to be constant in this study. Switches between daytime and shift work are rare. An initial validation study investigated the resulting misclassification (15).

For the period from 1995 onwards, in a sample of 921 production employees, the status of four of 324 daytime workers changed to shift work, and that of 24 of 597 shift workers to daytime work. There was no change for 893 (97%) of the employees (14). Information on shift status before 1995 is available only on paper.

The authors investigated a sample of 300 employees, 200 of whom worked shifts and 100 worked daytime hours on January 1, 1995. Their shift status was

recorded retrospectively for their whole working lives. The mean duration of misclassified shift status was estimated at 3.3% for daytime workers and 15.6% for shift workers. Both these validation studies suggest that misclassification has not substantially biased the study findings.

Statistical processing

The number of cancer cases observed and the number expected on the basis of incidence rates in the population of Rhineland-Palatinate were compared using standardized incidence rates (SIRs) and 95% confidence intervals (95% CIs).

Differences between cancer incidence among shift workers and daytime workers were investigated using Cox regression and reported as hazard ratios (HRs) with 95% confidence intervals. Adjustment was performed for the potential confounding factors of age and professional status. Lifestyle factors associated with high social status are known risk factors for prostate cancer. As used in earlier publications, professional status—categorized into skilled work/supervision and manual labor—was used as a proxy for social status. Smoking is not a known risk factor for prostate cancer and was included only in sensitivity analysis (23).

A dose–effect relationship between duration of employment in shift work and prostate cancer was investigated in two ways:

- Time-dependent dichotomous indicator variables: 20 years of employment or less versus more than 20 years of employment
- Further subdivision: less than 30 years, 30 to <35 years, 35 to <40 years, 40 to <45 years, 45 to <50 years, and 50 years or more of employment

To investigate a potential latency in the development of prostate cancer, a latency period of 20 years was used for sensitivity analyses; these were based on the study findings on breast cancer. All evaluations were performed using SAS 9.4 (24).

Results

The cohort included 27 828 employees. Two individuals with the same recorded beginning and end of employment dates were excluded. During the 10-year study period (270 068 person-years), 555 and 518 cases of cancer were observed in daytime and shift workers respectively, of which 191 and 146 respectively were prostate cancers (Table 2).

Data was successfully matched with that of the Rhineland-Palatinate Cancer Registry; this yielded only six uncertain cases, of which three were among the 337 cases of prostate cancer.

The majority of prostate cancer cases ($n = 322$; 95.5%) were observed in employees who had been employed for 20 years or longer. Stages T2 ($n = 216$; 64.1%) and T3 ($n = 71$; 21.1%) were the most frequently diagnosed. In the chi-square test there was no difference between the T stage distribution for daytime and shift workers in either manual ($p = 0.60$) or other ($p = 0.21$) workers ($p = 0.34$).

TABLE 2a

Distribution of markers in a cohort of shift and daytime workers in a large German chemical company

	Daytime workers		Shift workers	
	<i>n</i>	%	<i>n</i>	%
Individuals	15 219	54.7% of 27 828	12 609	45.3% of 27 828
Person-years	147 892.0		122 176.4	
Professional status				
Manual labor	7367	48.4	10 786	85.5
Skilled work/supervision	7852	51.6	1823	14.5
Type of activity				
Production	1569	10.3	10 837	85.9
Maintenance	5852	38.5	627	5.0
Other	7798	51.2	1145	9.1
Smoking				
Unknown	1706	11.2	55	0.4
Current smoker	4145	27.2	5350	42.4
Former smoker	4246	27.9	4561	36.2
Nonsmoker	5122	33.7	2643	21.0
Duration of employment (years)				
0 to <5	55	0.4	77	0.6
5 to <10	459	3.0	427	3.4
10 to <15	1048	6.9	1521	12.1
15 to <20	1677	11.0	2546	20.2
20 to <25	2730	17.9	2943	23.3
25 to <30	2125	14.0	2217	17.6
30 to <35	2402	15.8	1617	12.8
35 to <40	2065	13.6	797	6.3
40 to <45	1817	11.9	364	2.9
45 to <50	830	5.5	99	0.8
≥50	11	0.1	1	0.0
Living or deceased				
Deceased	370	2.4	339	2.7
Took part in census on December 31, 2009	14 294	93.9	11 752	93.2
Cancer cases				
Deceased	135	24.3	139	26.8
Living	420	75.7	379	73.2
Incident prostate cancer cases				
Stage T1	7	3.7	10	6.8
Stage T2	126	66.0	84	57.5
Stage T3	39	20.4	32	21.9
Stage T4	5	2.6	3	2.1
Stage TX	14	7.3	17	11.6

TABLE 2b

Distribution of markers in a cohort of shift and daytime workers in a large German chemical company

	Daytime workers		Shift workers	
	Median	Interquartile range	Median	Interquartile range
Year of birth	1959	1949 to 1967	1960	1950 to 1966
Year of entry	1978	1969 to 1987	1985	1976 to 1989
End of follow-up	2009	2009 to 2009	2009	2009 to 2009
Age on entry	17.0	15.0 to 20.0	23.0	18.0 to 28.0
Age at beginning of follow-up	40.5	32.5 to 50.5	39.5	33.5 to 49.5
Age at end of follow-up	50.5	42.5 to 59.5	49.5	43.5 to 59.5

Both daytime and shift workers had a higher incidence of prostate cancer than the general population (SIR = 1.44, 95% CI: 1.22 to 1.70; SIR = 1.51, 95% CI: 1.30 to 1.74). In both groups, the SIR for stage T1 prostate cancer or prostate cancer with no recorded stage was less than 1; for all other stages it was more than 1. The highest values recorded were for stage T2 (SIR = 2.05; 95% CI: 1.71 to 2.44 for shift workers; SIR = 1.73; 95% CI: 1.38 to 2.14 for daytime workers) (Table 3). The 20-year latency period used in analysis had little effect on the findings, as prostate cancer was diagnosed during the first 20 years of employment in only 15 employees.

Shift workers' risk of prostate cancer was no higher than that of daytime workers (HR = 0.93; 95% CI: 0.73 to 1.18) (Table 4). There was a non-significant increase in the risk of a diagnosis of stage T1 or T4 prostate cancer (HR = 1.26; 95% CI: 0.44 to 3.86 versus HR = 1.36; 95% CI: 0.25 to 6.18) and a decreased risk for stages T2 and T3 (HR = 0.84; 95% CI: 0.62 to 1.15 versus HR = 0.90; 95% CI: 0.53 to 1.52). Adjustment for smoking had little effect on the findings (HR = 0.88; 95% CI: 0.69 to 1.13). The 20-year latency period used in analysis had only a weak effect on the overall HR (HR = 0.89; 95% CI: 0.69 to 1.14) and stage-specific risk estimators.

In dose-effect analysis, the dichotomous indicator for duration of employment (less than 20 years versus 20 years or more) did not qualitatively change the findings. However, the risk of prostate cancer in those with longer employment histories was significantly higher than in those with shorter employment histories. Evaluation using further subdivision for duration of employment (Figure) indicates that the risk of stage T2 prostate cancer increases with duration of employment.

Conclusion

This research covered 337 cases in 27 828 employees and is therefore the largest cohort study on the risk of prostate cancer in shift and daytime workers to date. Tumor stage-specific comparisons were being presented for the first time. The cohort was put together in 1995 on the basis of personnel files and medical records (17) and since then has been followed actively. The health of the study participants was already well documented (13, 14).

TABLE 3

Standardized incidence rate (SIR) for prostate cancer in a cohort of shift and daytime workers in a large German chemical company

Prostate cancer, stage T	Daytime workers				Shift workers			
	Observed cases	Expected cases	SIR	95% CI	Observed cases	Expected cases	SIR	95% CI
Total	191	126.7	1.51	1.30–1.74	146	101.3	1.44	1.22–1.70
1	7	14.9	0.47	0.19–0.97	10	12.2	0.82	0.39–1.51
2	126	61.6	2.05	1.71–2.44	84	48.6	1.73	1.38–2.14
3	39	24.5	1.59	1.13–2.18	32	19.5	1.64	1.12–2.31
4	5	3.3	1.50	0.49–3.50	3	2.7	1.11	0.22–3.25
x	14	22.4	0.63	0.34–1.05	17	18.2	0.93	0.54–1.49
Sensitivity analysis based on 20-year latency period								
Total	189	121.4	1.56	1.34–1.80	133	92.2	1.44	1.21–1.71
1	7	14.3	0.49	0.20–1.01	10	11.3	0.89	0.43–1.63
2	125	58.8	2.12	1.77–2.53	73	43.9	1.66	1.30–2.09
3	38	23.4	1.62	1.15–2.23	31	17.7	1.75	1.19–2.49
4	5	3.2	1.57	0.51–3.67	3	2.4	1.25	0.25–3.65
x	14	21.6	0.65	0.35–1.09	16	16.9	0.95	0.54–1.54

95% CI: 95% confidence interval; SIR: Standardized incidence rate

TABLE 4

Hazard ratios (HRs) for the risk of incident prostate cancer in a cohort of shift and daytime workers in a large German chemical company

Model				Shift workers versus daytime workers			Skilled versus manual workers		Age		Smoking				Duration of employment	
											Current smokers		Former smokers			
	Individuals	Cases	HR	95% CI	p-value	HR	p-value	HR	p-value	HR	p-value	HR	p-value	HR	p-value	
Main model																
Total	27828	337	0.93	0.73–1.18	0.54	1.04	0.75	1.16	<0.01							
Stage 1	27828	17	1.26	0.44–3.86	0.67	0.55	0.31	1.22	<0.01							
Stage 2	27828	210	0.84	0.62–1.15	0.28	1.13	0.44	1.15	<0.01							
Stage 3	27828	71	0.90	0.53–1.52	0.69	0.83	0.50	1.18	<0.01							
Stage 4	27828	8	1.36	0.25–6.18	0.70	4.34	0.10	1.13	<0.01							
Stage X	27828	31	1.42	0.64–3.19	0.39	0.99	0.98	1.21	<0.01							
Main model adjusted for smoking																
Total	27828	337	0.88	0.69–1.13	0.33	1.03	0.82	1.16	<0.01	0.69	0.03	1.18	0.21	0.61	0.04	
Stage 1	27828	17	1.18	0.40–3.75	0.76	0.56	0.32	1.22	<0.01	1.13	0.85	1.05	0.94	0.69	0.75	
Stage 2	27828	210	0.80	0.58–1.09	0.16	1.11	0.51	1.15	<0.01	0.56	<0.01	1.24	0.20	0.52	0.04	
Stage 3	27828	71	0.87	0.51–1.48	0.60	0.84	0.51	1.18	<0.01	0.99	0.98	1.18	0.58	0.86	0.75	
Stage 4	27828	8	1.19	0.21–5.52	0.83	4.40	0.10	1.13	<0.01	0.77	0.78	0.71	0.67	0.00	0.99	
Stage X	27828	31	1.45	0.64–3.39	0.38	0.97	0.94	1.20	<0.01	0.73	0.56	1.08	0.86	1.04	0.96	
Main model assuming 20-year latency period																
Total	22562	322	0.89	0.69–1.14	0.35	1.09	0.51	1.16	<0.01							
Stage 1	22562	17	1.27	0.44–3.90	0.66	0.54	0.29	1.21	<0.01							
Stage 2	22562	198	0.77	0.56–1.06	0.11	1.19	0.27	1.16	<0.01							
Stage 3	22562	69	0.93	0.55–1.59	0.80	0.87	0.62	1.17	<0.01							
Stage 4	22562	8	1.37	0.25–6.19	0.69	4.18	0.11	1.12	0.01							
Stage X	22562	30	1.37	0.61–3.10	0.45	1.01	0.97	1.20	<0.01							
Main model adjusted for duration of employment (>20 years versus ≤20 years)																
Total	27828	337	0.95	0.75–1.21	0.69	0.99	0.92	1.16	<0.01					1.83	<0.01	
Stage 1	27828	17	1.35	0.47–4.12	0.58	0.48	0.21	1.20	<0.01					>1000	0.99	
Stage 2	27828	210	0.86	0.63–1.17	0.34	1.08	0.61	1.15	<0.01					1.54	0.11	
Stage 3	27828	71	0.92	0.54–1.55	0.76	0.80	0.40	1.17	<0.01					1.67	0.28	
Stage 4	27828	8	1.41	0.26–6.31	0.67	3.62	0.14	1.11	0.03					>1000	0.99	
Stage X	27828	31	1.46	0.66–3.27	0.35	0.91	0.82	1.20	<0.01					3.50	0.22	

95% CI: 95% confidence interval; HR: Hazard ratio

Hazard ratio (HR) for production workers who worked in a large German chemical company for 30 years or longer versus other production workers, adjusted for shift status

While the literature contains evidence that shift work that involves circadian disruption increases the risk of breast cancer, and some studies have reported an increased risk of prostate cancer, this study found no difference between shift and daytime workers (HR = 0.93; 95% CI: 0.73 to 1.18) (6–8, 25).

In this cohort there was a non-significantly increased risk of stage T1 and T4 prostate cancer in shift workers versus daytime workers, and a non-significantly reduced risk for stages T2 and T3. This pattern remained after additional adjustment for the confounding factors of smoking or duration of employment and when a latency period was assumed. Although the number of early stage T1 cancers was low and the SIR for shift and daytime workers was less than 1, this pattern indicated a group of shift workers who lived more health-consciously than their colleagues who worked during the day. The number of prostate cancers with a recorded T stage was 90.8% in this cohort and thus higher than the mean for Rhineland-Palatinate. Similarly, SIRs for prostate cancer of 1.44 and 1.56 in shift and daytime workers respectively versus the general population have already been reported (15). Both indicate detection bias as a result of the good medical care offered equally to all BASF employees. Prostate cancer screening is not actively offered to employees but can be performed on request (26). While increased SIRs for some cancers, such as cancer of the bladder, were due to occupational exposure in this cohort, no factors that might explain an increased risk of prostate cancer were recorded (27).

In addition to the size of the cohort, the strengths of this study included its documentation, based on person-

nel files and medical records. This means that recall bias can be ruled out. One feature of the cohort is the balanced numbers of daytime and shift workers from the same parts of the company and with the same working conditions, making them comparable in terms of risk profile, age distribution, and socioeconomic status. This maximized the power of internal comparisons and at the same time minimized the risk of bias caused by other work-related factors. In order to improve comparability further still, figures were adjusted for duration of employment, a proxy for work-related health risks resulting from chemical exposure, for example. Cancer cases were identified by matching data with the Rhineland-Palatinate Cancer Registry, which is complete and contains a high proportion of histologically confirmed cases. The tumor stage T was known in more than 90% of cases. This made stage-specific evaluation possible, so employees' health-related behavior and the effect of company medical prevention measures could be taken into account (28).

Data matching with the Rhineland-Palatinate Cancer Registry meant that only employees in the area covered by the registry could be included, and that cancer incidence could only be observed from the year 2000 onwards. A further weakness of the study results from shift status misclassification. As described in the *Methods* section, validation studies assessed shift status misclassification as low, so it could not have had a major effect on the study findings. More recently, a cohort of trainees with no adverse occupational factors has been put together, and the distribution of future shift and daytime workers has been investigated with regard to smoking and other cardiovascular risk factors (29).

In addition to the obvious sleep rhythm disruptions and associated effects on melatonin levels, shift work may have further effects on the risk of prostate cancer. It is suspected that vitamin D, cutaneous production of which requires ultraviolet radiation, inhibits prostate cancer (23). In addition, nutrition, particularly antioxidant intake, affects carcinogenesis and differs between daytime and shift workers (30, 31).

A working group of the International Agency for Research on Cancer (IARC) has debated the idea that duration of employment is a crude proxy for the cumulative effects of chronodisruption (32) and that shift work could be seen as a deviation from the natural day. Differences in chronoregulating genes may also play a role in carcinogenesis. Other authors argue that the individual chronotype or "social jetlag" is a more suitable measure of risk (3, 33). An initial cross-sectional study on this subject has recently been published (34).

The shift workers in this cohort worked according to two very similar forward-rotating shift patterns. The findings of this study cannot therefore simply be extrapolated to the variety of different shift patterns followed in Europe (32, 35).

Recording the individual chronotype is an approach for further investigation of this cohort. In the authors'

opinion, further follow-up of incidence rates in this still relatively young study population is important. Comparison of these findings with other shift patterns regarding prostate and other cancers may also be informative.

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Ethics Committee vote

This study received a positive vote from the Ethics Committee of the Rhineland-Palatinate State Medical Association.

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Conflict of interest statement

Dr. Yong is employed in the Medical Department of BASF SE.

Dr. Nasterlack was previously employed in the Medical Department of BASF SE. He holds shares in BASF SE.

Prof. Blettner has received fees for statistical processing of another study by BASF SE.

Dr. Hammer and Dr. Emrich declare that no conflict of interest exists.

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KEY MESSAGES

- Shift work that involves circadian disruption has been classified as a probable human carcinogen. This is indicated by animal experiments and mechanistic biological considerations. As yet there is little epidemiological evidence.
- Approximately 15 to 20% of the working population in industrial countries work shifts. Knowledge of the health effects of this are highly relevant to occupational health protection.
- In some studies, some of which are very large, a moderately increased risk of breast cancer has been observed in women who worked night shifts for many years.
- Initial studies on prostate cancer indicate an increased risk but are limited by sometimes very small case numbers and crude recording of exposure.
- The incidence of prostate cancer was investigated for the first time in a large, well documented cohort study involving 28 000 industrial workers. No difference was found between the risk for shift and daytime workers.

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