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Title Page –

Daily, monthly and seasonal variation in prostate specific antigen levels and the association with weather parameters.

David Connolly[1,3], Pim J. van Leeuwen[2], John Bailie[3], Amanda Black[4], Liam J. Murray[4], Patrick F. Keane[1], Anna Gavin[5].

[1]Department of Urology, Belfast City Hospital, [2]Erasmus University Medical Centre, Rotterdam, the Netherlands, [3]Department of Urology, Altnagelvin Hospital, Derry, [4]Cancer Epidemiology & Prevention Research Group, Queen's University Belfast, [5]Northern Ireland Cancer Registry, Queen's University Belfast.

Corresponding Author –
Mr. David Connolly,
Department of Urology,
Belfast City Hospital,
Lisburn Road,
Belfast,
Northern Ireland.
BT9 7AB.

E-mail - djconn76@hotmail.com
Telephone - (+44) 07817 209863 (Mobile)
Fax. - (+44) 02890 248017

Co-Authors:

Dr. Pim J. Van Leeuwen MD: Erasmus University Medical Centre, Rotterdam, the Netherlands. E-mail - p.vanleeuwen@erasmusmc.nl

Dr. John Bailie MB BCh: Department of Urology, Altnagelvin Hospital, Derry, Northern Ireland. E-mail – john.bailie@doctors.org

Dr. Amanda Black PhD: Cancer Epidemiology & Prevention Research Group, Queen's University, Belfast, Northern Ireland. E-mail – amanda.black@qub.ac.uk

Prof. Liam J. Murray MD: Cancer Epidemiology & Prevention Research Group, Queen's University, Belfast, Northern Ireland. E-mail – l.murray@qub.ac.uk

Mr. Patrick F. Keane FRCS (Urol): Department of Urology, Belfast City Hospital, Belfast, Northern Ireland. E-mail – patrick.keane@belfasttrust.hscni.net

Dr. Anna Gavin FFPHM: Northern Ireland Cancer Registry, Queen's University, Belfast, Northern Ireland. E-mail – a.gavin@qub.ac.uk

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Abstract

Prostate-specific antigen (PSA) levels have shown daily and seasonal variation, although data are conflicting regarding the season with higher PSA levels and the clinical relevance of this. We assessed the correlation of total PSA levels with meteorological data on a daily, weekly, monthly and seasonal basis. Data from 53 224 men aged 45-74 years, with an initial PSA <10.0ng/ml were correlated with temperature (^{o}C), duration of bright sunshine (hours) and rainfall (mm). There was seasonal variation in PSA levels, with median PSA being higher in spring compared to other seasons (1.18 vs. 1.10ng/ml, p=0.004). Seasonal variation was not apparent when PSA levels were age-adjusted (p=0.112). Total PSA was not correlated with daily, weekly or monthly hours of sunshine, rainfall nor mean temperature. In contrast, age-adjusted PSA varied with weekday, with higher PSA levels on Thursday and Friday compared to other days (1.16 vs. 1.10ng/ml respectively). On multivariate analysis, only age predicted for PSA levels >3.0ng/ml. In conclusion, PSA levels did show seasonal variation although there was no direct correlation between PSA and any meteorological parameter. The degree of seasonal variation is small and the decision to proceed to prostate biopsy should be independent of season or weather parameters.

Keywords: Age; PSA; Season; Variation; Weather.

Introduction

Prostate specific antigen (PSA) remains the best available biomarker for the early detection of prostate cancer.[1] One of the main limitations to the accuracy of PSA is its inherent variability,[2] with many factors known to cause transient elevations in PSA that are unrelated to prostate cancer.[3-6] As part of this variability, PSA has been shown to vary by season, with two studies from the French and Spanish sections of the European Randomized Study of Screening for Prostate Cancer (ERSPC) having contrasting results.[7,8] Specifically, Luján Galán et al.[7] found a non-significant trend towards higher PSA levels during the autumn and winter, whilst Salama et al.[8] found that PSA levels were higher during the summer, with a positive correlation between PSA level and insolation (hours of bright sunshine). The current study aimed to assess if the seasonality of PSA continued in a large non-screening population, and to examine the correlation of total PSA with meteorological data on a daily, weekly, monthly and seasonal basis.

Subjects and Methods

Study Participants

All men, aged 45-74 years, with an initial PSA <10.0 ng/ml, measured during a weekday in Northern Ireland (NI) between 1st January, 2002 and 31st December, 2006 were identified from a regional database of PSA tests.[9-11] Initial PSA data only were included, whilst men with a prior diagnosis of prostate cancer were excluded.

Weather data for NI were obtained from the UK Met Office (http://www.metoffice.gov.uk/climate/uk/datasets/index.html). Weather information including monthly minimum, maximum and mean temperatures (^{o}C), duration of bright sunshine (hours), actual rainfall (mm) and mean wind speed (knots) were obtained from January 2002 until December 2006. Daily meteorological data were available for 2006 only.

To assess if the weather parameters influenced the number of men who theoretically would be referred for biopsy if screening were performed, the number of men with a serum PSA ≥3.0ng/ml was calculated for each month.

Statistical Analysis

Variables are expressed as median and mean with 95% confidence intervals (CI). For statistical comparison, PSA values were logarithmically transformed to obtain a normal distribution. Weather parameters were normally distributed and so were not similarly transformed. Relationships were tested by the Pearson's product correlation coefficient. Multivariate linear and logistic regression was used to test the relation of meteorological data with PSA and a PSA cut-off of 3.0ng/ml. A p-value <0.05 was considered significant. All analyses were performed with the Statistical Package for the Social Sciences software, version 16.0.

Ethical Approval

All patient identifiable information was removed before the research team accessed the data used in this study, and no patient contact was made during the study. Therefore, ethical approval was not sought.

Results

53 224 men were included. Overall, total PSA correlated with age ($r=0.34$, $p<0.001$), with mean and median PSA levels increasing with age category (Table 1). The number and percentage of men with PSA levels above 3.0ng/ml also increased with increasing age ($p<0.001$). There was seasonal variation in PSA levels, with median PSA levels being higher in spring compared to other seasons (1.18 vs. 1.10ng/ml, $p=0.001$). Mean age at initial PSA testing was slightly higher in springtime compared to other seasons (59.7 vs. 59.4 years respectively, $p=0.075$). Consequently, seasonal variation in PSA was not apparent when PSA levels were age-adjusted ($p=0.112$). The monthly mean and median PSA levels, as well as the proportion of men with PSA levels above 3.0ng/ml are graphically illustrated in Figure 1. In contrast, age-adjusted PSA levels did vary by weekday, with PSA levels on Thursday and Friday being higher than on Monday, Tuesday and Wednesday (median 1.16 vs. 1.10ng/ml respectively, $p=0.004$).

As demonstrated in Figure 2, meteorological data showed monthly variation in hours of bright sunshine, mean temperatures and rainfall (95% CI: sunshine 93.3–117.5 hours,

temperature 8.5°C-10.5°C, rainfall 84.4–103.8 mm). Actual hours sunshine and mean temperatures were correlated ($r=0.60$, $p<0.001$), with a negative correlation between sunshine and rainfall ($r=-0.362$, $p<0.001$).

Overall, for the years 2002-2006, the age-adjusted total PSA was not correlated with monthly hours of sunshine ($r=-0.004$, $p=0.429$), mean temperature ($r=-0.005$, $p=0.282$) nor rainfall ($r=-0.001$, $p=0.935$). For 2006, the correlation between the age-adjusted PSA level and daily and weekly meteorological data was tested. No correlation was found for sunshine ($r=-0.005$, $p=0.570$), mean temperature ($r=-0.002$, $p=0.844$), rainfall ($r=0.001$, $p=0.931$), nor wind speed ($r=0.007$, $p=0.382$). When analyses were confined to men with PSA levels <4.0ng/ml, again no correlation was found between age-adjusted PSA levels and sunshine ($r=-0.003$, $p=0.603$), temperature ($r=0.004$, $p=0.445$) nor rainfall ($r=-0.001$, $p=0.829$).

Since PSA ≥3.0ng/ml is a widely used cut-off for prostate biopsy, multivariate logistic regression analysis was used to establish if men were at higher risk of having PSA ≥3.0ng/ml in relation to age and meteorological variation. Significant association was found for age [odds ratio (OR): 1.091, 95%CI 1.087-1.095, $p<0.001$], but not for sunshine (OR 1.00, 95%CI 0.99-1.01, $p=0.789$), mean temperature (OR 0.993, 95%CI 0.983-1.002, $p=0.123$), nor rainfall (OR 1.00, 95%CI 0.99-1.01, $p=0.827$).

Discussion

This study has confirmed that there is seasonal variation in total PSA levels, with men in the current study having higher PSA levels in spring compared to other seasons. Seasonal variation was however not apparent when PSA levels were age-adjusted. Further, there was no direct correlation between PSA and any single meteorological parameter. In contrast, there was variation in age-adjusted PSA level by weekday, with total PSA being higher on a Thursday or Friday than other days, suggesting that there may be other social factors responsible for this variation as opposed to it simply being weather related. Finally, although the variations in PSA level noted in the current study, namely a median difference of 0.08ng/ml by season and 0.06ng/ml by weekday respectively, are statistically significant, they are not clinically significant. Therefore, contrary to the recommendations by Salama et al.[8] there is no benefit in repeating an abnormal PSA level, and the decision to proceed to prostate biopsy should be independent of season or climatic conditions.

Strengths of the current study are the large number of participants and its population-based design. The PSA data included represents all initial PSA tests <10.0ng/ml, performed in NI between 2002 and 2006 – this is therefore a heterogeneous group containing all men undergoing PSA testing, irrespective of their symptoms. Previous studies have demonstrated that the majority of men in NI had PSA testing performed for urinary symptoms (64.9%), 16.9% had testing for symptoms suggestive of advanced cancer such as bone pain, whilst only 18.0% were asymptomatic - this therefore more

likely represents a standard clinical population than a pure screening study.[9] Further, meteorological data was available at a daily level as opposed to simply a seasonal or monthly level, allowing more in depth analysis.

There are a number of notable limitations. Firstly, the data are retrospective. Ideally, the effect of weather parameters on PSA levels should be assessed by a prospective longitudinal study. Given the small variations in PSA levels noted in the current study, this would require a large number of participants, with data also being collected on other factors which may affect PSA levels such as sexual activity. As this would require significant time and resources, and the impact on clinical practice is likely to be minor, the current study design may be an appropriate alternative. Secondly, clinical information was not available for men, which prevents inferences being made about how factors such as the reason for PSA testing, family history, medications, rectal examination findings, or prostate volume may have influenced PSA levels. Thirdly, different PSA assays were used during the study period, which, given their inherent variability, might not provide results that are directly comparable. Analyses were repeated assessing each individual year when assays may have changed and no significant correlation was identified between weather parameters and PSA. Further, previous analyses of the NI PSA database have not shown any systematic bias in PSA results from any laboratory.[9-11] Other limitations of the data in the NI PSA database have previously been discussed.[9-11] Additionally, regional weather data only are presented. NI is a small region with similar weather patterns throughout the province,

therefore local differences in weather parameters are unlikely to be significant. Furthermore, NI is a temperate region with lower temperatures and levels of sunshine than many countries; the PSA changes demonstrated may only be applicable to areas with similar climatic conditions. Finally, due to the possibility of there being a lag time between periods of bright sunshine to changes in PSA, the analyses were repeated assessing a lag time of one week and one month. Similar results i.e. no correlation was identified between any weather parameter and PSA levels.

The results of the current study differ from recent studies that demonstrated higher PSA levels in autumn or winter and in summer.[7,8,12] Luján Galán et al.[7] assessed PSA levels in 2147 men participating in the Spanish section of the ERSPC, and correlated these with meteorological data. They found a non-significant trend towards higher PSA levels in the autumn and winter, with age and temperature being independent predictors of having a PSA level ≥3.0ng/ml on multivariate analysis. As the magnitude of the PSA changes was small, Luján Galán et al.[7] did not recommend any changes to biopsy indication based on climatic parameters. In contrast, using a similar study design in 8644 men from the French section of the ERSPC, Salama et al.[8] found higher PSA levels during the summer, with a positive correlation between PSA and insolation. This resulted in a 23% higher risk of being referred for prostate biopsy during the summer, based on the ERSPC cut-off of 3.0ng/ml. Salama et al. therefore recommended 'confirming any isolated test result before biopsy, even more so if this was obtained in summer'.[8] Veith et al.[12] assessed changes in PSA in men on active surveillance for

prostate cancer, and found a lower increase or even a decrease in PSA levels in spring compared to other seasons. This was attributed, as it was in the study by Salama et al.[8] to be due to the potentially positive effects of vitamin D on prostate biology. The current study, in a much larger and heterogeneous population, showed higher PSA levels in spring with no correlation between PSA and meteorological parameters. One possible explanation for the differing results may be the different populations; certainly the population in NI is different from that in the ERSPC, with less than 20% of men being asymptomatic at the time of PSA testing.[9] However, the populations in the French and Spanish studies should have been similar, with both meeting the inclusion criteria for the ERSPC, and so, comparable results would have been expected. Another possible reason could be the temperate climate in NI compared to France or Spain. If PSA levels were related to insolation, then there may be a minimum level of sunshine exposure that is required to cause an elevation of PSA, which is not met in NI. As demonstrated in Figure 2, even at peak levels of sunshine, the duration was much lower in NI (150 to 200 hours per month) compared to the French study (300 to 350 hours per month).[8] Again, if this effect were true, then an even greater difference would have been expected in the Spanish study,[7] and in fact, the converse was true, PSA levels were higher in cold weather conditions.

A more likely explanation to the differing results between the studies may be that other unmeasured factors were involved which may cause higher PSA levels and are related to season. Firstly, as the seasonal variation was not apparent when PSA levels were

age-adjusted, this may simply be an age-related phenomenon i.e. slightly older men were more likely to attend for PSA testing during springtime. Further, the variation in age-adjusted PSA levels in NI by weekday suggests that there may be social reasons involved as opposed to a true biological basis. One possible factor is sexual behaviour and ejaculation. Ejaculation has been shown to cause transient rises of PSA.[3,4] Tchetgen et al.[3] demonstrated in 64 men aged 49–79 years, that PSA had increased by 0.8ng/ml at 1 hour, 0.3ng/ml at 6 hours and 0.2ng/ml at 24 hours post-ejaculation. They also found that higher baseline PSA values tended to increase by more following ejaculation and that there was a significant positive correlation between the patients' age and the PSA increase following ejaculation.[3] Similarly, Herschman et al.[4] found in 20 men with mean age 59 years, a mean increase in PSA of 0.3ng/ml at 1 hour, 0.1ng/ml at 6 hours and 0.1ng/ml at 24 hours post-ejaculation. Sexual behaviour in humans does show seasonal variation.[13-17] This is apparent in many European countries,[13] with peak conception rates occurring in April / May. Conception rates also correlate with increasing exposure to sunlight and with temperature.[14,15] Further, the frequency of sexual activity, rate of sexually transmitted diseases and the sale of contraceptives are all seasonal,[16] with Carlsen et al.[17] demonstrating higher rates of ejaculation during springtime in Danish men. Therefore, seasonal variation in PSA levels may be a reflection of the variation in ejaculation frequency in the studied populations. Interestingly, Roenneberg and Aschoff found that conception rates are decreased at extremes of temperature,[14] which, if there was an associated decrease in frequency of ejaculation, may explain the lower levels of PSA in Spain during the summer and the subsequent higher levels in autumn and winter.[8]

A similar argument can be made for physical activity to be a contributing factor to seasonal variation in PSA. Physical activity, particularly bicycle riding, can be associated with a transient rise in PSA,[18,19] particularly in older men and those with elevated baseline PSA levels. Further, physical exercise has been shown to have seasonal variability, with decreased levels of exercise during the winter or in extremes of weather.[20] This has been shown specifically in older people, with exercise levels being independently correlated with day length, sunshine and mean temperature.[21]

Irrespective of the cause of seasonal variation of PSA, the clinical application of this is more straightforward. As demonstrated in the previous studies and illustrated in Figure 1,[7,8,12] the actual variation in mean and median PSA by season is of a small magnitude, and although statistically significant, is not clinically significant. If the decision to proceed to prostate biopsy is based on the underlying risk of prostate cancer as opposed to a PSA value being above or below an arbitrary cut-off, then these variations in PSA by season or weekday are irrelevant. Contrary to the recommendations by Salama et al.[8], there is therefore no benefit in repeating an abnormal PSA level, and the decision to proceed to prostate biopsy should be independent of season or climatic conditions.

In conclusion, this study has confirmed that there is seasonal variation in total PSA levels, with men in the current study having higher PSA levels in spring compared to other seasons. As the seasonal variation was not apparent when PSA levels were age-

adjusted, this may simply be an age-related phenomenon, and appears more likely to be related to social factors as opposed to climatic conditions. The magnitude of variations in PSA level by season or weekday is small and should not influence the decision to proceed to prostate biopsy.

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Conflict of interest

There is no conflict of interest for any author.

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Tables

Table 1 Patient characteristics; age, total prostate specific antigen (PSA) and number with PSA>3.0ng/ml by age category

Age (years)	Number of men (%)	Total PSA (ng/ml)		PSA >3.0ng/ml (%)
		Mean (95% CI)	Median (IQR)	
45-50	8971 (16.9)	1.02 (0.99–1.04)	0.70 (0.50-1.11)	371 (4.1)
51-55	10167 (19.1)	1.26 (1.24–1.29)	0.90 (0.50-1.50)	787 (7.7)
56-60	11108 (20.6)	1.56 (1.53–1.59)	1.00 (0.60-1.90)	1422 (12.8)
61-65	9604 (18.2)	1.82 (1.78–1.85)	1.20 (0.70-2.30)	1698 (17.7)
66-70	7541 (14.2)	2.20 (2.15–2.24)	1.50 (0.80-2.91)	1877 (24.9)
71-75	5833 (11.0)	2.48 (2.43–2.54)	1.80 (0.90-3.50)	1791 (30.7)

Figure legends

Figure 1 Variation in total prostate specific antigen (PSA) levels and percentage of men with PSA ≥3.0 ng/ml by month.

Figure 1a Total PSA

Figure 1b Percentage with PSA>3.0ng/ml

Figure 2 Monthly variation in actual sunshine, mean temperature and rainfall.

Figure 2a Actual sunshine (hours)

Figure 2b Temperature (^{o}C)

Figure 2c Rainfall (mm)

Abbreviations used

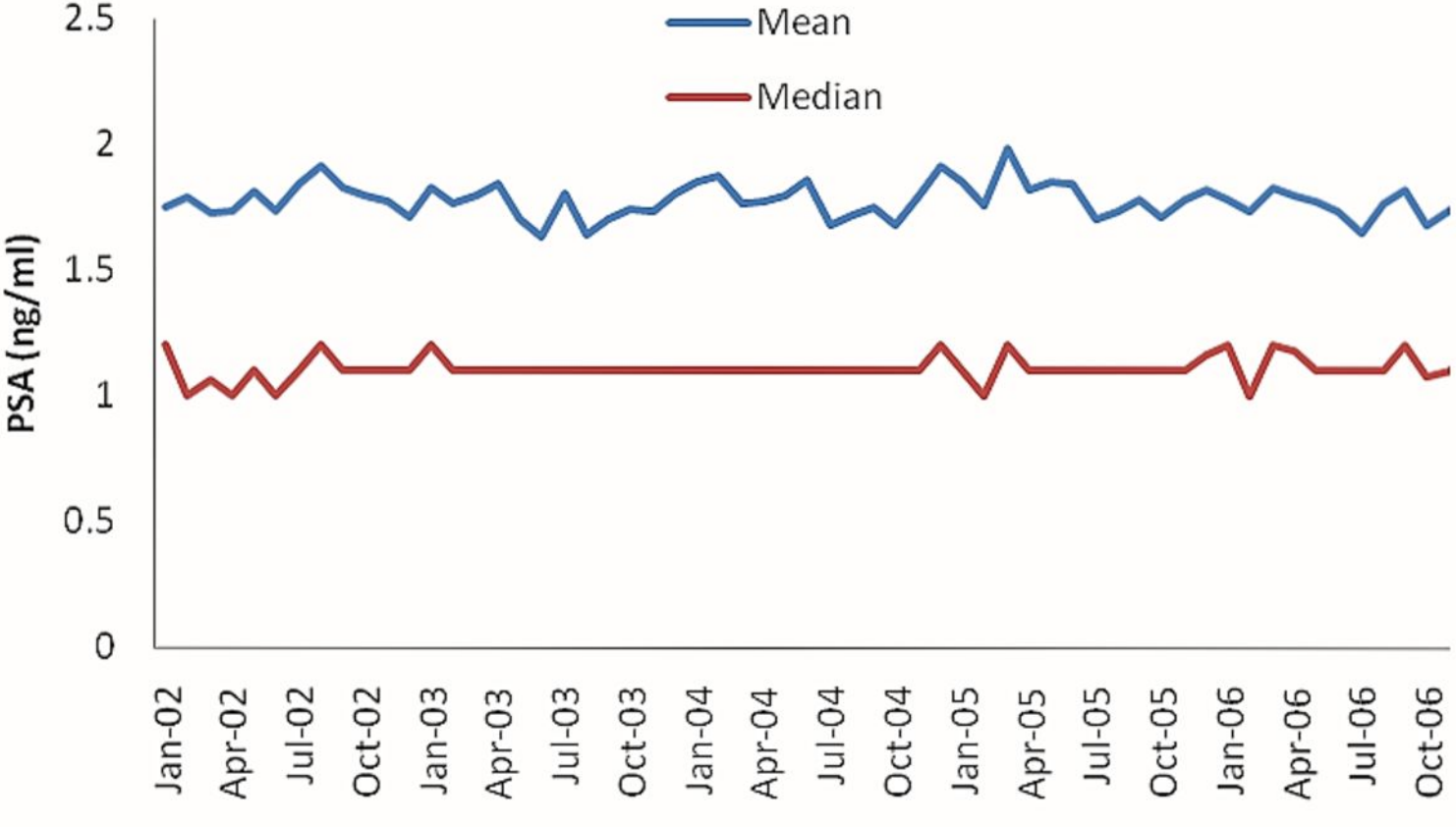
PSA = Prostate specific antigen

ERSPC = European Randomized Study of Screening for Prostate Cancer

NI = Northern Ireland

CI = Confidence interval

OR = Odds ratio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Median
PSA (ng/ml)
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2
1.5
1
0.5
0
Jan-02
Apr-02
Jul-02
Oct-02
Jan-03
Apr-03
Jul-03
Oct-03
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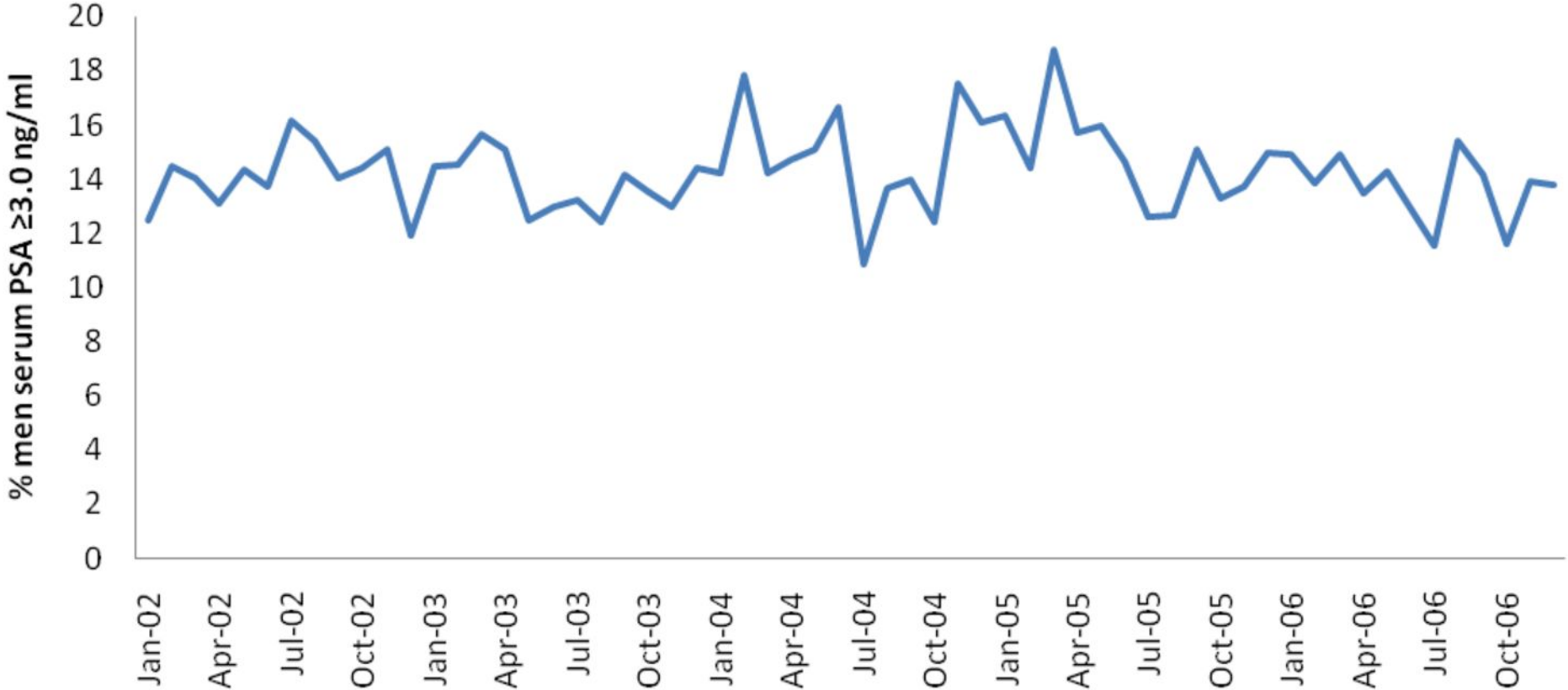
Jul-06
Oct-06


% men serum PSA ≥3.0 ng/ml
20
18
16
14
12
10
8
6
4
2
0
Jan-02
Apr-02
Jul-02
Oct-02
Jan-03
Apr-03
Jul-03
Oct-03
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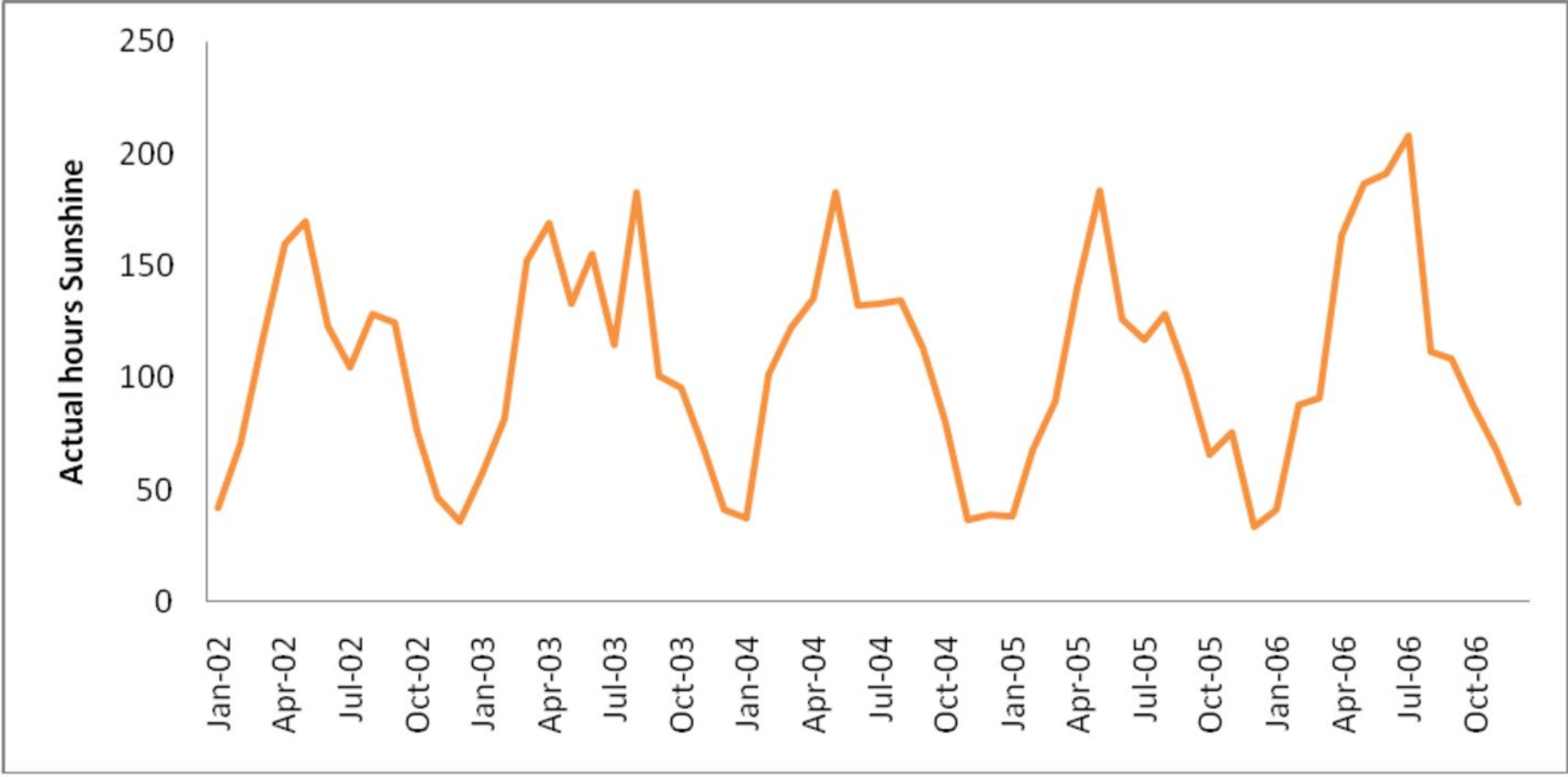
Jul-06
Oct-06


Actual hours Sunshine
250
200
150
100
50
0
Jan-02
Apr-02
Jul-02
Oct-02
Jan-03
Apr-03
Jul-03
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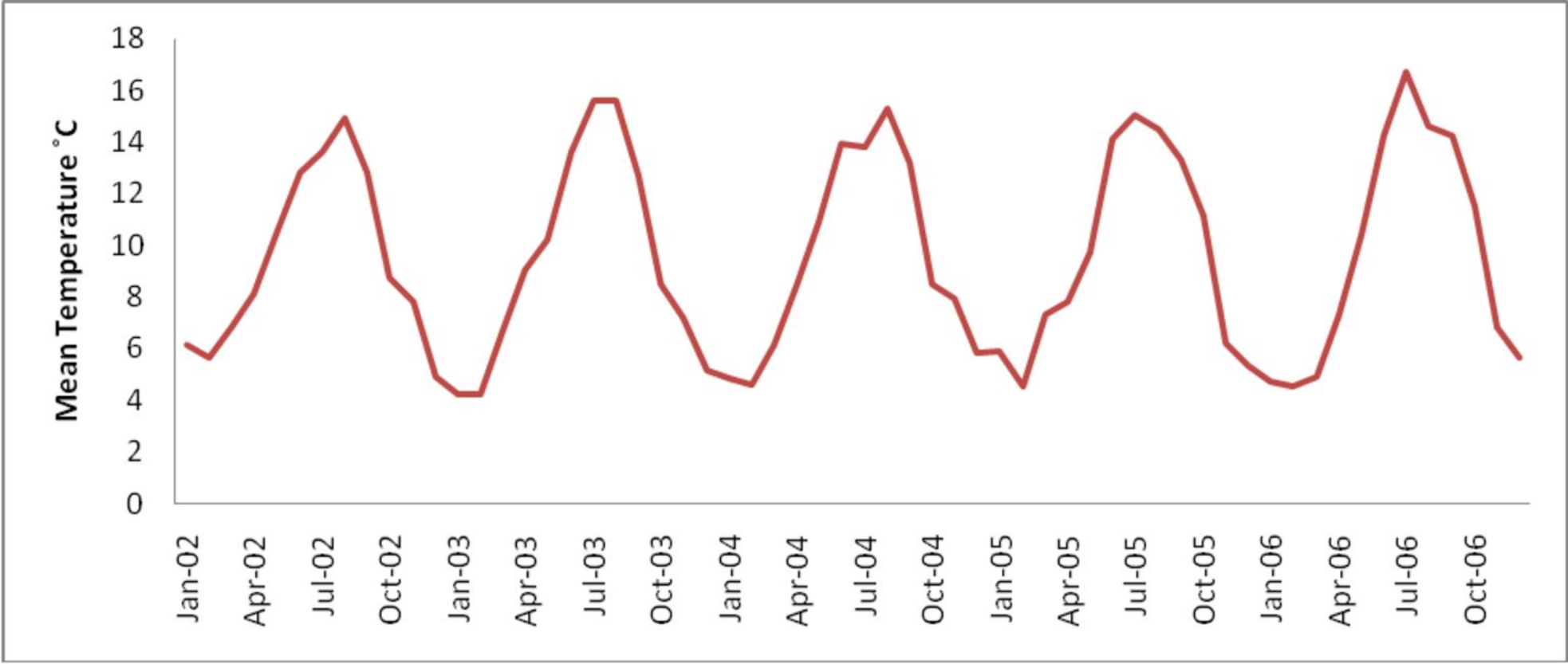
Jul-06
Oct-06


Mean Temperature °C
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16
14
12
10
8
6
4
2
0
Jan-02
Apr-02
Jul-02
Oct-02
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Jul-03
Oct-03
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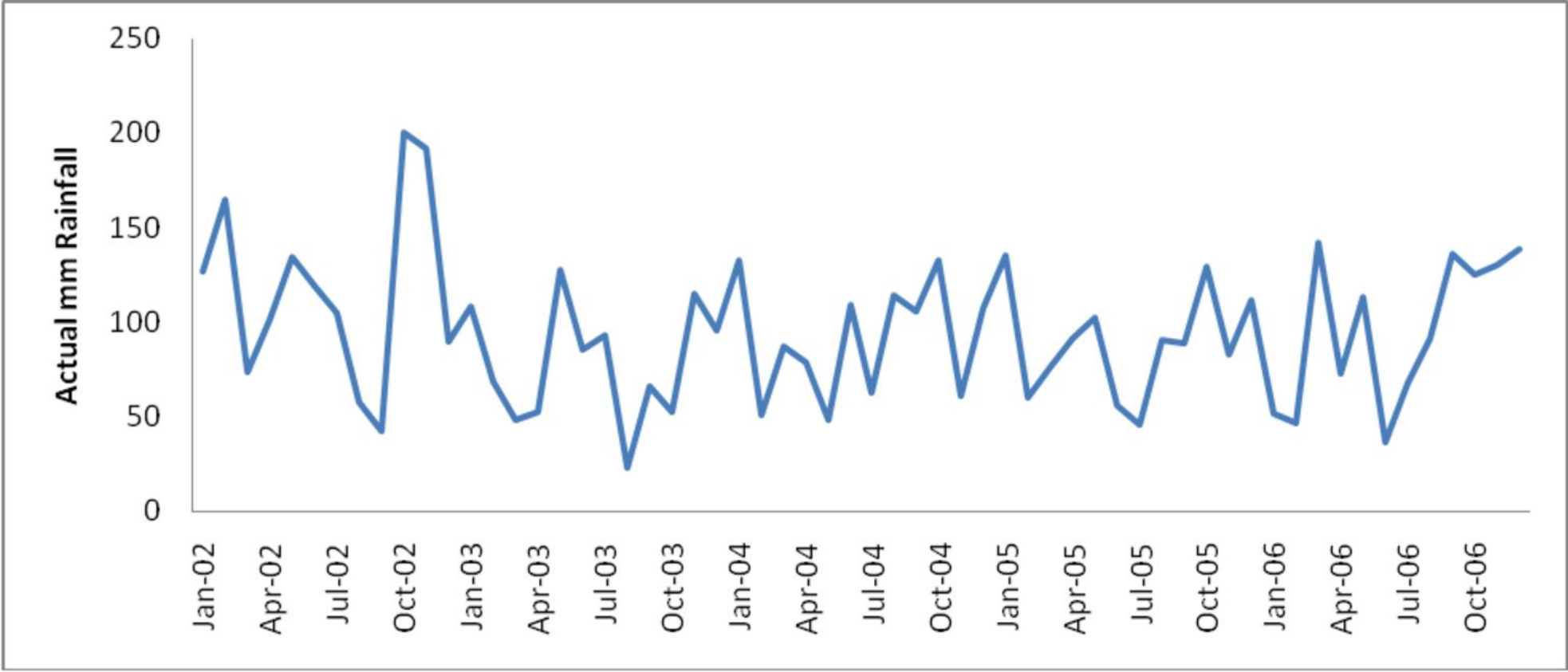
Jul-06
Oct-06


Actual mm Rainfall
250
200
150
100
50
0
Jan-02
Apr-02
Jul-02
Oct-02
Jan-03
Apr-03
Jul-03
Oct-03
Jan-04
Apr-04
Jul-04
Oct-04
Jan-05
Apr-05
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