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Prostate-specific antigen testing for prostate cancer: Depleting a limited pool of susceptible individuals?

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Abstract

After the introduction of the prostate specific antigen (PSA) test in the 1980s, a sharp increase in the incidence rate of prostate cancer was seen in the United States. The age-specific incidence patterns exhibited remarkable shifts to younger ages, and declining rates were observed at old ages. Similar trends were seen in Norway. We investigate whether these features could, in combination with PSA testing, be explained by a varying degree of susceptibility to prostate cancer in the populations. We analyzed incidence data from the United States' Surveillance, Epidemiology, and End Results program for 1973–2010, comprising 511,027 prostate cancers in men 40 years old, and Norwegian national incidence data for 1953–2011, comprising 113,837 prostate cancers in men 50 years old. We developed a frailty model where only a proportion of the population could develop prostate cancer, and where the increased risk of diagnosis due to the massive use of PSA testing was modelled by encompassing this heterogeneity in risk. The frailty model fits the observed data well, and captures the changing age-specific incidence patterns across birth cohorts. The susceptible proportion of men is 39.9 % (95 % CI 38.2; 41.6 %) in the United States and 30.4 % (95 % CI 28.9; 32.0 %) in Norway. Cumulative incidence rates at old age are unchanged across birth cohort exposed to PSA testing at younger and younger ages. The peaking cohort-specific age-incidence curves of prostate cancer may be explained by the underlying heterogeneity in prostate cancer risk. The introduction of the PSA test has led to a larger number of diagnosed men. However, no more cases are being diagnosed in total in birth cohorts exposed to the PSA era at younger and younger ages, even though they are diagnosed at younger ages. Together with the earlier peak in the age-incidence curves for younger cohorts, and the strong

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familial association of the cancer, this constitutes convincing evidence that the PSA test has led to a higher proportion, and an earlier timing, of diagnoses in a limited pool of susceptible individuals.

Keywords

Prostate cancer; Susceptibility; Frailty; PSA test

Introduction

Prostate cancer is the most common male cancer in the western world, and is typically diagnosed at ages >60 years [1]. In the areas of the Surveillance, Epidemiology, and End Results (SEER) program in the United States (US), the incidence rate of prostate cancer rose during 1973–1992, with a much steeper increase from 1987 onwards [2]. The Norwegian incidence rate rose steadily since the 1950s, with a steeper increase in the 1990s [3]. The large increase in the incidence rate during the past 25 years has largely been attributed to expanding use of prostate-specific antigen (PSA) testing [1].

Cancer risk is highly heterogeneous. Many studies indicate a large and mostly unexplained variation in cancer susceptibility; see Aalen et al. [4] for a review. Frailty models, from the statistical field of survival analysis [5–7], have become a useful tool in modeling cancer incidence rates under the assumption of a strong heterogeneity in risk [8–15]. The underlying idea is that the peaks in the age-incidence curves are reflections of selection effects in the population. Individuals with the highest susceptibility, or frailty, develop the disease relatively early, causing increased incidence rates. After some time, fewer of the highly susceptible individuals are left in the at-risk population, and the incidence rate drops. However, cancers that have been studied using frailty models are mostly those with peaking age-incidence rates at younger ages, such as testicular cancer [8]. For many other types of cancer, the incidence rates increase by age before they level off or even decline at old age (>80 years). This leveling off may be related to less intensive diagnostic work-up in these patients, or cell senescence, i.e., cells replicate less frequently at older ages, thus reducing the chance of mutations or other events promoting cancer development [16–18]. However, because of widespread opportunistic PSA testing for prostate cancer, the explanation of a decreasing incidence rate at old age may be more complex than hitherto recognized.

The age-specific incidence rate of colorectal cancer peaks at an age >85 years. Despite that the peak occurs at such an advanced age, it has nevertheless been viewed as the result of an underlying heterogeneity in colorectal cancer risk [9, 15]. The pre-PSA age-specific incidence patterns of prostate cancer had similar features as those of colorectal cancer. However, the introduction of PSA testing on a large scale represents a natural experiment that may produce more reliable estimates of susceptibility than for colorectal cancer. PSA testing not only lowers the age of prostate cancer diagnosis, but may also lead to a concurrent reduction in incidence rates at older ages. This would suggest the existence of a (possibly large) group of individuals with low susceptibility remaining after individuals at high susceptibility have been depleted (i.e. diagnosed) earlier as a result of extensive PSA testing.

The objective of this study is to use the heterogeneity in risk of prostate cancer to explain the shape of the incidence rates by age in the US and in Norway. This is done by developing and applying a frailty model. The use of the PSA test is more widespread, and its implementation occurred more rapidly, in the US compared to Norway. The two populations thus differ in their shift to earlier diagnosis of prostate cancer. By analyzing these two contrasting populations, we may gain important knowledge about the heterogeneity in susceptibility to prostate cancer.

Data material

The SEER program is a collection of nine registries covering about 10 % of the US population [19], and include 511,315 prostate cancers diagnosed in 1973–2010 at ages 0–84 years old (born during 1889–2010), in 448,107,857 man-years at risk. We only consider men reaching an age 40 years, which include 511,027 prostate cancers in 165,784,054 man-years at risk among men born during 1889–1970. The SEER data have high quality [20, 21]. The Cancer Registry of Norway is a nation-wide registry with an almost 100 % completeness [22]. The Norwegian data include 113,837 prostate cancer cases diagnosed during 345,507,983 man-years among those 50–95 years old in 1953–2011, born during 1858–1961.

Methods

We use a two-step estimation procedure. The model is described below, with details given in the Supplement. In the first step, we only consider the ages of birth cohorts that have not (yet) been subject to extensive PSA testing. A given birth cohort consists of individuals born in a single year. In the second step, we assess the impact of the extensive PSA testing era.

We chose 1986 as the start of the PSA era in the SEER areas [23]. In Norway, the PSA test was introduced later into common practice [24, 25], and 1989 is chosen as the start of the PSA era here. Furthermore, PSA testing in the oldest part of the populations seem to have increased less than in those younger [26, 27]. However, there are also indications that the proportion of PSA tested among older men is increasingly catching up to middle aged men [28, 29]. A possible reduction of the effect of being in the PSA era, due to less testing at old age, is allowed for in the model.

First-step estimation: The pre-PSA era

In the first step, we estimate a general frailty model. The frailty, or susceptibility, is compound Poisson (cP) distributed. The cP distribution has a discrete part in zero and a continuous part for positive frailty, and is frequently used in frailty modeling [5, 7, 9–12]. Hence, the proportion of the population that is susceptible to be diagnosed with the cancer may be estimated. Note that a more reasonable interpretation of the non-susceptible subgroup in practice is that they have a very low risk. The general risk pattern for all members of the population is described through a basic hazard rate on Weibull form, due to the Armitage-Doll framework [30],

$$\lambda(t) = \begin{cases} 0, & t < \tau \\ k(t - \tau)^{k-1}, & t \geq \tau \end{cases}, \quad (1)$$

where t is age, and τ is set to 40 years since prostate cancer very rarely occurs before that age. The k parameter has traditionally been interpreted as the number of rate limiting steps in carcinogenesis. The frailty variable is multiplied with $\lambda(t)$ to calculate the individual hazard rate. That is, the general risk pattern is regulated up or down according to the individual degree of susceptibility. The observed incidence rate in the population is the net result of all individual risk patterns.

Prostate cancer incidence rates increased in the SEER areas and Norway also before the PSA era. We model this by letting the probability of being susceptible increase with birth cohort up to those born in 1902 for both countries (1858–1902 in Norway, and 1889–1902 in the SEER areas). Due to the limited amount of pre-PSA data points for younger birth cohorts, the modeled age-specific incidence rates do not change after 1902. Note, however, that all pre-PSA data points are used in the estimation of the remaining model parameters. For a detailed description of how the proportion susceptible men were calculated from the estimated parameters, see the Supplement. All other parameters are estimated jointly for the two countries. The estimated proportions of susceptible individuals should be seen as a combination of actual underlying biological susceptibility and the ability to detect them. The increase in the US pre-PSA incidence rate has to a large extent been explained by incidentally detected prostate cancers associated with increased use of transurethral resection [23, 31], a procedure whose usage was dramatically reduced after 1986 [23]. Increased awareness of prostate-related symptoms is also a likely contributor to the pre-PSA increase in Norway and the US, as well as the more frequent use of surgical treatment for benign prostate hyperplasia [32].

Maximum likelihood estimation is performed to estimate parameters and their covariance matrix, from which 95 % confidence intervals (CIs) are calculated.

Second-step estimation: The PSA era

In the second step of the estimation, we assess the effect of the extensive PSA testing (SEER: from 1986, Norway: from 1989), with the cohorts born from 1903 (SEER) and 1895 (Norway) being exposed to PSA testing. This is modelled by multiplying the basic hazard rate in Expression 1 with the function

$$h_i(t) = \begin{cases} 1, & t \leq s_i \\ 1+r_i(t-s_i), & s_i < t \leq s_i+\beta \\ 1+r_i\beta, & s_i+\beta < t \leq \tau_{2,i} \\ 1+r_i\beta - r_{2,i}(t-\tau_{2,i}), & \tau_{2,i} < t \leq \tau_{2,i}+\beta_{2,i} \\ 1+r_i\beta - r_{2,i}\beta_{2,i}, & t > \tau_{2,i}+\beta_{2,i} \end{cases}, \quad (2)$$

to obtain the modified basic hazard rate for birth cohort i as

$$\lambda_i(t) = \lambda(t)h_i(t). \quad (3)$$

The function $h_i(t)$ may be viewed as a hazard ratio, comparing a PSA era exposed individual to an unexposed individual, given the same value of the frailty. $h_i(t)$ is shown in Fig. 1 and the parameters are summarized in Table 1. Here, s_i is the age at which individuals born in year i enter into the PSA era or 40 years, whichever is largest. The function is increasing linearly with age from age s_i . The slope of this increase, r_i , is estimated for each birth cohort. The increasing effect of the PSA era lasts for β years, which is estimated for all birth cohorts jointly. Thus, after age $s_i + \beta$ the hazard ratio is no longer increasing. Depending on s_i and β , there are four possible shapes of the hazard ratio function for a birth cohort (panels 1–4, Fig. 1), according to the following scenarios:

1. Those born in the earliest birth years that became exposed to the PSA era (at old age) would only be followed for a short period of time. If $s_i + \beta$ is larger than the maximum follow-up age, τ_3 (SEER: $\tau_3 = 84$ years, Norway: $\tau_3 = 95$ years), then the linear increase of the hazard ratio last for $\tau_3 - s_i$ years. This illustrated in panel 1 of Fig. 1.
2. If age $s_i + \beta$ is less than the maximum follow up age, but larger than 70 years, we let the effect of being in the PSA era wear off linearly with age from age $s_i + \beta$ to age τ_3 . The slope of this decrease, $r_{2,i}$ is estimated for each birth cohort, except those falling into scenario 1. This is illustrated in panel 2 of Fig. 1.
3. If age $s_i + \beta$ is less than 70 years, the hazard ratio stays constant between $s_i + \beta$ and 70 years of age. The hazard ratio decreases linearly from age 70 years to age τ_3 , with slope $r_{2,i}$. This is illustrated in panel 3 of Fig. 1.
4. If individuals enter into the PSA era at an age less than 40 years, the linear increase of the hazard ratio starts at 40 years. Otherwise similar to scenario 3. Cohorts born from 1946 (SEER) and 1949 (Norway) fall into this scenario, illustrated in panel 4 of Fig. 1.

The age at which the effect of being in the PSA era starts to decrease, is denoted $\tau_{2,i}$ in Fig. 1, and the time between the maximum follow-up age, τ_3 , and $\tau_{2,i}$ is denoted $\beta_{2,i}$. The maximum value of the hazard ratio is $1 + r_i\beta$ (panels 1, 2 and 3, Fig. 1), while its value is $1 + r_i\beta - r_{2,i}\beta_{2,i} > 0$ at age τ_3 . An $r_i = 0$ means no effect of the PSA era on cohort i .

This approach should account for the larger number of latent cancers in birth cohorts that were old when the PSA test was introduced, and the possible reduction of PSA testing of old men in younger birth cohorts [2, 26, 27]. Age 70 was chosen according to PSA testing guidelines [28, 33, 34].

Further details on the second-step model are given in the Supplement. The parameter estimates from the first-step (pre-PSA era) estimation are treated as constants in the second step (PSA era). To carry the uncertainty from the first-step estimation over to the second step, a parametric bootstrap procedure is applied. One thousand samples are drawn from the normal distribution with mean and covariance matrix equal to the parameters and covariance

found in the first step. The second-step maximum likelihood estimation is done for each of the 1000 sets of step-one parameters, and 95 % bootstrap CIs are found by the 2.5 and the 97.5 percentiles of the resulting distributions of the step-two parameters.

Results

Figure 2 shows age standardized, with respect to the world population [35], incidence rates in the SEER areas and Norway with sharp increases in the 1990s. Figure 3 presents the observed age-specific incidence rate for each decade of diagnosis using the available data for the SEER areas and Norway. Clear shifts to younger ages at diagnosis are seen in both populations.

The pre-PSA era

Pre-PSA era parameter estimates are given in Supplementary Table 1. The k parameter (often interpreted as the number of rate-limiting steps in the carcinogenic process) was 4.55 (95 % CI 4.52; 4.58). In the SEER areas, the proportion of susceptible men increased from 25.4 % (95 % CI 24.2; 26.6 % for those born in 1889 to 39.9 % (95 % CI 38.2; 41.6 %) for those born in 1902 onwards. The estimated proportion of susceptible Norwegian men increased from 14.9 % (95 % CI 14.1; 15.7 % for those born in 1858 to 30.4 % (95 % CI 28.9; 32.0 %) for those born in 1902 onwards. The fit of the model to the observed incidence rate is shown for each birth cohort (1858–1945) in Supplementary Film 1. The model fits the data well also for those born after 1902, when the proportions of susceptible individuals are no longer increasing, and where individuals will eventually enter into the PSA era at some later age.

The PSA era

No effect of entering the PSA era was found for birth cohorts 1895–1903 for Norway (i.e. $r_i = 0$ for these birth cohorts, p values >0.05 by likelihood ratio tests). Note, however, that these individuals were all 83 years old when the PSA test was introduced, an age group not likely subject to extensive PSA testing [25]. For all other birth cohorts, a significant effect of the PSA testing era was found.

The multiplicative effect on the basic hazard rate (displayed in Fig. 1) was increasing linearly for $\beta = 6.9$ (95 % CI 6.9; 7.1) years in the SEER areas and $\beta = 19.1$ (95 % CI 19.0; 19.3 years in Norway. The estimated slopes, the r_i s, of this increase are shown, with 95 % CIs, in Fig. 4 for all birth cohorts i exposed to the PSA era. These estimates were fluctuating somewhat for the oldest birth cohorts, before stabilizing around 0.30–0.35 for the SEER area and around 0.05–0.15 for Norway. The function plotted in Fig. 1 may be seen as a hazard ratio, comparing an exposed to an unexposed (to the PSA era) individual, given the same frailty. The term $1 + r_i\beta$ is the maximum value of this hazard ratio. Choosing a value of r_i of, say, 0.3 for the SEER areas and 0.1 for Norway, this term would be 3.1 and 2.9, respectively. This means that at its full effect, the PSA era has a similar impact on the hazard rate in the two areas. However, it takes almost three times as long for the hazard ratio to reach this value in Norway, compared to the SEER areas (Norway: 19.1 years, SEER: 6.9 years). All estimated PSA era parameters are given in Supplementary Table 2 (SEER) and 3 (Norway).

The model allowed for a possible linear decrease in the multiplicative effect of PSA testing on the basic hazard rate after age $\tau_{2,i} = \max(70; s_i + \beta)$ years (panels 2, 3 and 4, Fig. 1). The estimated slopes, the $r_{2,s}$, of these decreases are given in Supplementary Table 2 for the SEER areas. For Norway (with $\beta = 19.1$) there were too few data points available after this age to estimate such a slope. Hence, no reduction is modeled for Norway and the function in panel 2, 3 and 4 of Fig. 1 is constant after age $\tau_{2,i}$.

Figure 5 shows the final model fit to the observed incidence rate for three selected birth cohorts. The age-specific incidence rates start to increase at earlier ages as we move to the younger birth cohorts (from 1908 to 1918 and, finally, 1938) that entered into the PSA era at younger ages, and peaks are emerging. The fits to the data of each birth cohort are given in Supplementary Film 2 (SEER) and 3 (Norway). The model fits the observed data well for all birth cohorts, for both the SEER areas and Norway.

Figure 6 shows the model-based cumulative incidence rate for five birth cohorts (1910, 1914, 1918, 1922 and 1924), selected because data were available for most parts of the age range studied. Considering the good fit of the model to the age-specific incidence rates, these should reflect the actual cumulative incidence rates well. Even though these birth cohorts entered into the PSA era at increasingly younger ages, and are diagnosed earlier, the cumulative incidence rates at high ages does not increase.

Discussion

We have shown that a model assuming an underlying heterogeneity in prostate cancer susceptibility captures the shape of the age-specific incidence rates in the US and Norway well. Our findings suggest that there is a limited pool of individuals that is susceptible to prostate cancer. PSA testing has led to a larger degree of depletion of this group. Furthermore, as PSA testing starts at increasingly younger ages, this pool of individuals is diagnosed at earlier ages, leaving few susceptible individuals in the at-risk populations at older ages.

Genome-wide association studies have revealed multiple loci, mostly of low penetrance, associated with prostate cancer risk [36]. Furthermore, there is a strong familial association of prostate cancer risk, with an approximately 3-, 8- and 18-fold increased risk if one, two or three brothers are affected, respectively [37]. Aalen et al. discussed how such a strong familial gradient implies that the distribution of risk is very skewed across the population [4]. This strong heterogeneity in risk, which goes beyond what can be explained by observed risk factors, is exactly what is modeled in the present paper.

Understanding the issue of unobserved variations in cancer risk is important. It is part of the biological understanding of cancer and can be related to (epi)genetics or simply random phenomena producing inequality, as discussed in Aalen et al. [4]. When attempting to understand the causes of cancer, the strongly varying susceptibility is obviously of importance. This may also impact how cancer is prevented; rather than a population-wide screening approach, one should have a more individual focus on screening with those at high risk or susceptibility for prostate cancer being screened most frequently (if they can be

identified). Genomic biomarkers being revealed for prostate cancer may make this achievable in the foreseeable future [38]. This is part of the drive towards personalized medicine. The present study is not designed to shed light on the likely over-diagnosis due to PSA testing [39], which would require data on disease severity. Nevertheless, our results indicate that the PSA test could continue to be a helpful tool if its use is much more targeted. The familial disease history of the individual could e.g. be one suitable tool for determining whether PSA testing should be recommended or not.

In a recent review, 36 and 51 % of undiagnosed Caucasian-Americans and African-Americans, respectively, aged 70–79 years had a pre-PSA era prostate cancer found at autopsy [40]. Although clinically diagnosed cancers are not included, this indicates that not all men are necessarily prone to develop this cancer form. We estimated proportions of men susceptible to prostate cancer (SEER: 40 %; Norway: 30 %) based on incidence data. However, the autopsy results also include cases that would never have been clinically diagnosed. Even though our susceptibility estimates and the autopsy results are not directly comparable, and our estimates would be higher if containing clinically undetectable cancers, this indicates that our results are reasonable. Note also that not all susceptible men will necessarily develop the cancer. Differences in ethnic compositions of the two populations, with blacks having higher incidence [41], and differences in classifications of new disease [42], may explain part of the difference in susceptibility estimates between the SEER areas and Norway. In any case, this difference reflects that the incidence rate has, historically, been higher in the SEER areas than in Norway (as seen in Fig. 2).

The decline of the prostate cancer age-specific incidence rate at old age has, in the pre-PSA era, been considered the result of lack of diagnostic work-up among elderly people and/or cell senescence at old age. If all men had a fairly similar risk of developing prostate cancer, one would not expect this decline to move to younger ages. Since the peaks in the age-specific incidence rates have moved to younger ages, explanations relating to old age are no longer applicable. We argue that an underlying heterogeneity in the risk of this cancer could be the reason for the decline in the age-specific incidence rate at old age.

Although recommendations go against PSA testing at old age [33, 34], it is unclear if this is followed in practice [2, 26–29, 43]. Nevertheless, less testing at old age serves as a third explanation to the declining incidence rate at old ages. We incorporated this into our model by allowing the effect of being in the PSA era to decrease after 70 years (at the earliest). This significantly improved the model fit for the SEER data at these ages, but the overall tendencies in how the peak in the age-specific incidence curve moved to younger ages, were also captured without modeling this feature. As we move to younger cohorts, it becomes increasingly likely that individuals at older ages have already been PSA tested at younger ages. This could explain a less frequent testing among the older men. If a high rate of PSA testing is maintained at old ages, this would further strengthen the notion of heterogeneity in risk. However, if the PSA test at old age is not the first one, it is more likely to be negative (assuming that positive tests precipitate some kind of treatment) compared to those receiving the test for the first time. Hence, the effect of being in the PSA era should decrease also if this is the case, since we are then repeatedly PSA testing individuals with a very low

susceptibility being left in the at-risk population. Hence, PSA testing in old men may not be worthwhile.

Clearly, from the sharp increases in the incidence rates in the 1990s, PSA testing has led to a larger number of diagnoses in birth cohorts exposed to the PSA testing compared to those who were not. However, comparing birth cohorts that became exposed to PSA testing at younger and younger ages, the plots of the cumulative incidence rates (Fig. 6) indicate that there are not more cases being diagnosed in total even though the timing of diagnoses are moved to younger ages. This is a strong indication that there is a limited group of men with a detectable prostate cancer. Earlier detection of these must lead to a later decline in the incidence rate, because there are fewer of these left in the at-risk population.

Even though the hazard ratios at their maximum values are similar for the two countries, this level is reached much faster in the SEER areas. Our results thus reflect that PSA testing was more rapidly taken into clinical practice, and widespread use, in the US than in Norway [25, 44–46].

In summary, we have applied a frailty model to analyze incidence data from the US and Norway, two contrasting populations when it comes to PSA test usage. A good fit to the age-incidence curves was achieved for both countries. There is convincing evidence that there is a strong heterogeneity in prostate cancer risk: 1) The extensive PSA testing after the mid-1980s has driven the peak in the incidence rate in these populations towards younger ages. 2) The cumulative incidence rates at old ages are virtually constant for birth cohorts entering into the PSA era at increasingly younger ages. 3) Furthermore, there is a strong familial association in the risk for the cancer. PSA testing has thus led to a higher proportion of diagnoses, compared to the pre-PSA era, and earlier diagnoses as the exposure (to PSA testing) has begun at younger ages. Hence, PSA testing has led to higher degree of depletion of a limited pool of susceptible individuals. This is a feature of prostate cancer that has not, to our knowledge, been addressed already to any large degree.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

The function given in Expression 2, which is multiplied with the basic hazard rate in Expression 1, to model the impact of extensive PSA testing. The function may be viewed as a hazard ratio, comparing an exposed (to the PSA era) to an unexposed individual with the same frailty. The parameters are described in Table 1 and the text

Fig. 2. Age standardized incidence rates of prostate cancer, with respect to the world standard population [35], per 100,000 man-years with respect to calendar year for the SEER areas (1973–2010) and for Norway (1953–2011). To also include cases diagnosed before age 50, the Norwegian curve was constructed using the NORDCAN database [47]

Fig. 3.

Left The incidence rate of prostate cancer per 100,000 man-years with respect to age (40–84 years) for each decade of the SEER data. *Right* The incidence rate of prostate cancer per 100,000 man-years with respect to age (50–95 years) for each decade of the Norwegian data

Fig. 4.

The estimated r_i s, the slopes of the multiplicative effect of being exposed to the PSA testing regimen (see Expression 2 and Fig. 1 for details), with 95 % bootstrap confidence intervals for each birth cohort, for the US' SEER areas and Norway

Fig. 5.

Observed and modeled incidence rate of prostate cancer with respect to age for the birth cohorts 1908, 1918 and 1938. For the observed incidence rate, the ages at which the birth cohort is exposed to PSA testing or not, are indicated (as PSA or pre-PSA, respectively).

Left panel The SEER areas. *Right panel* Norway

Fig. 6.

Cumulative incidence rate of prostate cancer with respect to age for the birth cohorts 1910, 1914, 1918, 1922 and 1926, estimated from the model. The *lines* are solid at ages where they are based on observed data, and dashed at ages where the model is extrapolated. *Left panel* The SEER areas. The birth cohorts enter into the PSA era at 76, 72, 68, 64 and 60 years of age (represented by the *diamond symbols*), respectively. *Right panel* Norway. The birth cohorts enter into the PSA era at 79, 75, 71, 67 and 63 years of age (represented by the *diamond symbols*), respectively

Table 1

Description of the parameters used to describe the function that models the impact of the extensive PSA testing from the late 1980s. The function is plotted in Fig. 1

Parameter (combination)	Description
s_i	The age at which birth cohort i enters into the PSA era, or 40 years, whichever is largest
β	The amount of time (after s_i) there is an linearly increasing effect of being in the PSA era
r_i	The slope of the linearly increasing effect from s_i
$s_i + \beta$	The age at which there is no longer an increasing effect of the PSA era
$\tau_{2,i}$	Age at which the effect of being in the PSA era starts to “wear off”, is equal to either $s_i + \beta$ or 70 years (if $s_i + \beta < \tau_3$)
τ_3	The maximum follow-up age. SEER: 84 years, Norway: 95 years
$\beta_{2,i}$	The amount of time between $\tau_{2,i}$ and τ_3
$r_{2,i}$	The slope of the linearly decreasing effect of being in the PSA era between $\tau_{2,i}$ and τ_3
$1 + r_i\beta$	The maximum value of the hazard ratio for birth cohort i
$1 + r_i\beta - r_{2,i}\beta_{2,i}$	The value of the hazard ratio at τ_3

Note that parameters β , r_i and $r_{2,i}$ are estimated. Furthermore, there is one set of parameters for either of the two areas, SEER and Norway