Deriving benefit of early detection from biomarker-based prognostic models

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Appendix A1. Alternative biomarker model

In this section we re-derive some results from the manuscript, but under an alternative mean function describing the biomarker trajectory. Assume that the mean function is $m(t) = \exp\{\theta_1 + \theta_2 t + \theta_3 (t - a_O)^+\}$, where t is time and it relates to subject's age. To make the intercept interpretable we assume $t = 0$ refers to a known reference age, say 20 years old. Thus, $\exp(\theta_1)$ is the mean PSA level at the reference age. Next, $\exp(\theta_2)$ refers to the pre-onset biomarker change rate while $\exp(\theta_1 + \theta_2)$ refers to the post-onset biomarker change rate.

Under the above mean function model, we can re-write lead time in terms of the biomarker change rate and the biomarker levels at a_A and a_E as $\ell = a_A - a_E = \frac{\log\{m(a_A)\} - \log\{m(a_E)\}}{\theta_2 + \theta_3}$.

We can re-write the biomarker level at early detection as

$$m(a_E) \;=\; m(a_A)\exp(-(\theta_2 + \theta_3)\ell).$$

Thus, the hazard function h_2 implies that the hazard ratio for survival benefit takes the form

$$HR_2 \;=\; \exp[\beta\{m(a_E) - m(a_A)\}] \;=\; \exp[\beta m(a_A)\{\exp(-(\theta_2 + \theta_3)\ell) - 1\}],$$

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while under hazard function h_3,

$$HR_3 = \exp[\beta_1 m(a_A)\{\exp(-(\theta_2+\theta_3)\ell) - 1\} - \beta_2 \ell].$$

Using the PSA model, we can re-express age at early detection a_E as

$$a_E = a_O \left[\frac{\theta_3}{\theta_2+\theta_3}\right] + \left[\frac{\log\{m(a_E)\} - \theta_1}{\theta_2+\theta_3}\right].$$

The expression for $RHR_3(m_0, m_1)$ uses ages at early detection a_{S_1} and a_{S_0} obtained using the above equation when considering PSA threshold levels m_1 and m_0, respectively.

The following Figure 1 and Table 1 show results under the alternative biomarker mean model. We use $\theta_1 = 0.30$, $\theta_2 = 0.03$, and $\theta_3 = 0.10$ or 0.20; that is, at the reference age, the biomarker level is $\exp(0.30) = 1.35$ ng/mL. The biomarker changes at a rate equal to 3% per year before onset. After onset, the rate of change is increased by 10% or 20% per year.

The results are similar to those discussed in the manuscript.

[Table 1 about here.]

[Figure 1 about here.]

Appendix A2. Weibull model

Assume a Weibull baseline hazard function so that $h_0(v) = \eta\gamma^\eta v^{\eta-1}$, where $\eta > 0$ and $\gamma > 0$. When $\eta = 1$, this reduces to a exponential survival model. The Weibull baseline hazard function decreases in v when $0 < \eta < 1$ and increases in v when $\eta > 1$.

Assuming a Weibull baseline hazard function implies that time T to disease-specific death is Weibull with parameters η and $\gamma \exp(X'\beta/\eta)$. For any $p \in (0,1)$, let $Q(p;T) = S^{-1}(p)$ denote the quantile function. In the above, $S^{-1}(\cdot)$ is inverse of the survival function. Under the Weibull distribution,

$$Q(p; T \mid X) = \left\{\frac{-\log(p)}{\gamma^\eta \exp(X'\beta)}\right\}^{1/\eta}.$$

Utilizing the above quantile function one can show that, under the Weibull model, the condition for screening benefit simplifies to

$$\exp\left\{\frac{(X_E - X_A)'\beta}{\eta}\right\} + \frac{\ell}{\{-\log(p)\}^{1/\eta}}\gamma \exp\left(\frac{X_E'\beta}{\eta}\right) < 1.$$

Just as seen under the exponential model, we note that $\exp\{(X_E - X_A)'\beta\} < 1$. Thus, given X_E and X_A, the conditional is more likely to be met when γ is small or ℓ is small.

Appendix A3. Conditional survival

Let $S(\cdot)$ and $\tilde{S}(\cdot)$ denote, respectively, the *unconditional* and *conditional* survival functions. The corresponding hazard functions are $h(\cdot)$ and $\tilde{h}(\cdot)$.

We note that

$$\tilde{S}(u) \;=\; P(T_D > u \mid T_D > \ell) = \begin{cases} 1, & \text{if } u < \ell \\ \frac{P(T_D>u)}{P(T_D>\ell)}, & \text{if } u \geq \ell \end{cases}.$$

Equivalently, with a change of variable with $v = (u - \ell)$,

$$\tilde{S}(\ell + v) \;=\; \begin{cases} 1, & \text{if } v < 0 \\ \frac{S(\ell+v)}{S(\ell)}, & \text{if } v \geq 0 \end{cases}.$$

It follows that the hazard function for the conditional survival is

$$\tilde{h}(u) = \begin{cases} 0, & \text{if } u < \ell \\ h(u), & \text{if } u \geq \ell \end{cases} \quad \overset{v=u-\ell}{\equiv} \quad \tilde{h}(\ell + v) = \begin{cases} 0, & \text{if } v < 0 \\ h(\ell + v), & \text{if } v \geq 0 \end{cases}.$$

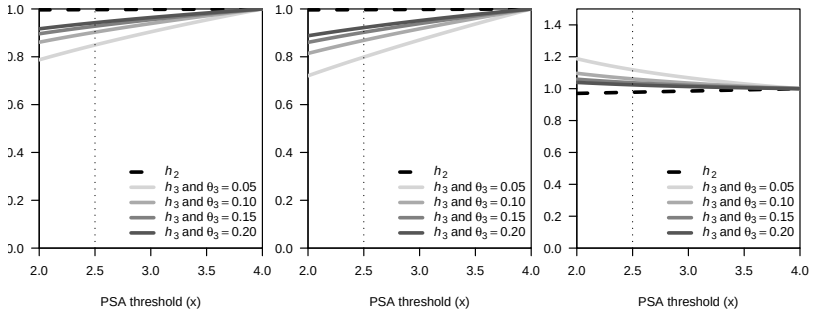

Figure 1. Sensitivity analysis to a different mean model for PSA. Relative hazard ratios (RHRs) for selected early detection rules under exponential survival overall grade (left panel) or stratified by low grade (middle panel) and high grade (right panel). The RHRs compare hazard ratios derived under hazard functions h_2 and h_3 when the PSA threshold for early detection is in the range of 2.0 to 4.0 ng/mL relative to the rule that uses PSA threshold of 4.0 ng/mL.

Table 1

Sensitivity analysis to a different mean model for PSA. Lead times (ℓ) and hazard ratios (HRs) when actual diagnosis occurs at a PSA threshold of $m(a_A) = 10.0$ ng/mL and early diagnosis occurs at a PSA threshold of $m(a_E) = 2.5$ or 4.0 ng/mL under hazard functions h_2 (using PSA only) and h_3 (using PSA and age). Results assume an exponential survival model.

Hazard Function	θ_2	$\hat{\beta}_{PSA}$	$\hat{\beta}_{AGE}$	$m(a_E)$	ℓ	HR	SE	95% CI
Overall								
h_2	0.10	0.002		2.50	10.66	0.99	0.00	[0.98, 0.99]
	0.10	0.002		4.00	7.05	0.99	0.00	[0.98, 1.00]
	0.20	0.002		2.50	6.03	0.99	0.00	[0.98, 0.99]
	0.20	0.002		4.00	3.98	0.99	0.00	[0.98, 1.00]
h_3	0.10	0.002	0.03	2.50	10.66	0.74	0.09	[0.58, 0.92]
	0.10	0.002	0.03	4.00	7.05	0.82	0.06	[0.70, 0.95]
	0.20	0.002	0.03	2.50	6.03	0.84	0.05	[0.73, 0.95]
	0.20	0.002	0.03	4.00	3.98	0.89	0.04	[0.81, 0.96]
Low Grade								
h_2	0.10	0.002		2.50	10.66	0.99	0.01	[0.97, 1.00]
	0.10	0.002		4.00	7.05	0.99	0.01	[0.98, 1.00]
	0.20	0.002		2.50	6.03	0.99	0.01	[0.97, 1.00]
	0.20	0.002		4.00	3.98	0.99	0.01	[0.98, 1.00]
h_3	0.10	0.002	0.04	2.50	10.66	0.66	0.13	[0.45, 0.94]
	0.10	0.002	0.04	4.00	7.05	0.76	0.09	[0.59, 0.96]
	0.20	0.002	0.04	2.50	6.03	0.79	0.08	[0.64, 0.96]
	0.20	0.002	0.04	4.00	3.98	0.85	0.06	[0.74, 0.97]
High Grade								
h_2	0.10	0.015		2.50	10.66	0.89	0.05	[0.80, 0.99]
	0.10	0.015		4.00	7.05	0.91	0.04	[0.84, 0.99]
	0.20	0.015		2.50	6.03	0.89	0.05	[0.80, 0.99]
	0.20	0.015		4.00	3.98	0.91	0.04	[0.84, 0.99]
h_3	0.10	0.014	-0.02	2.50	10.66	1.15	0.23	[0.77, 1.67]
	0.10	0.014	-0.02	4.00	7.05	1.08	0.14	[0.82, 1.39]
	0.20	0.014	-0.02	2.50	6.03	1.03	0.12	[0.81, 1.30]
	0.20	0.014	-0.02	4.00	3.98	1.00	0.08	[0.85, 1.18]