Published in final edited form as:

Stat Med. 2009 November 20; 28(26): 3276–3293. doi:10.1002/sim.3705.

Survival attributable to an exposure

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SUMMARY

In the survival analysis context, when an intervention either reduces a harmful exposure or introduces a beneficial treatment, it seems useful to quantify the gain in survival attributable to the intervention as an alternative to the reduction in risk. To accomplish this we introduce two new concepts, the attributable survival and attributable survival time, and study their properties. Our analysis includes comparison with the attributable risk function as well as hazard-based alternatives. We also extend the setting to the case where the intervention takes place at discrete points in time, and may either eliminate exposure or introduce a beneficial treatment in only a proportion of the available group. This generalization accommodates the more realistic situation where the treatment or exposure is dynamic. We apply these methods to assess the effect of introducing highly active antiretroviral therapy for the treatment of clinical AIDS at the population level.

Keywords

attributable risk function; survival analysis; parametric models; generalized gamma distribution; product limit estimate

1. INTRODUCTION

The attributable risk (AR) is widely used to provide a measure of the public health significance of an association between exposure to a risk factor (E) and occurrence of a disease (D). For simplicity, we initially consider only the case where the exposure has two levels, exposed (E_1) and unexposed (E_0). The exposure may represent something actually present in the environment that increases the risk of disease, or may represent the lack of a beneficial treatment that also increases disease risk relative to the treated population. Whether exposure represents the presence of risk or the absence of benefit, we assume that $P(D|E_1) > P(D|E_0)$. The AR combines a measure of association between exposure and disease, $RR = P(D|E)/P(D|\bar{E})$, with the rate of exposure in the population, $P(E_1)$, as follows:

$$\begin{aligned} AR &= [P(D) - P(D | E_0)] / P(D) = 1 - P(D | E_0) / P(D) \\ &= P(E_1)(RR - 1) / [P(E_1)(RR - 1) + 1] \end{aligned} \quad (1)$$

The AR is typically interpreted as the proportion of disease that could be prevented by elimination of exposure to the risk factor. Note that this is distinct from what is sometimes called the preventable fraction [1], which is defined by $PF = [P(D|E_1) - P(D)]/P(D|E_1)$; see Section 4.2. For additional discussion and references see Rothman and Greenland [1], Gefeller [2] and Uter and Pfahlberg [3].

If the measure of disease occurrence is $F_D(t) = P(T \leq t)$, the cumulative event rate at time t measured from a well-defined origin (e.g. infection with a virus), then the attributable risk becomes dynamic, and its behavior over time may provide information about effects of the timing of interventions, or may suggest approaches that are more appropriate in the context of survival. In Section 2, we consider the natural extension of the AR in the survival context, the attributable risk function, as well as alternatives based on the hazard function. We show that the behavior of the attributable risk function is unsatisfactory in some respects. We therefore introduce two new definitions in Section 3, the attributable survival, and attributable survival time, which are based on the attribution of survival rather than failure, and characterize their properties. We conclude that the proposed measures are useful in the context of survival analysis.

As a generalization, in Section 4 we allow the distribution of exposure to change at discrete points in time and extend the various definitions to this case, giving additional insight into the different approaches to attribution. Section 5 first considers the simple example of two exponential distributions; the new approach is then applied at the population level to study the beneficial effects of highly active antiretroviral therapy on survival after a diagnosis of clinical AIDS, using both parametric models and nonparametric methods.

2. THE ATTRIBUTABLE RISK FUNCTION AND HAZARD-BASED ALTERNATIVES

2.1. The attributable risk function

We begin with the simple case of a population composed of individuals who are either always exposed (E_1) or never exposed (E_0). The proportion of exposed individuals is $0 < \pi = P(E_1) < 1$, with failure distribution $P(T \leq t | E_1) = F_1(t)$, while the proportion unexposed is $1 - \pi$, with distribution $P(T \leq t | E_0) = F_0(t)$. Time to event in the overall population then has a mixture distribution, $F(t) = \pi F_1(t) + (1 - \pi)F_0(t)$, representing the proportion of disease at time t in the entire population. In survival analysis it is more natural to work with the corresponding survival functions, $S_1(t)$, $S_0(t)$ and $S(t) = \pi S_1(t) + (1 - \pi)S_0(t)$. In the setting of a deleterious exposure, which could be the absence of a beneficial treatment, we must have $F_0(t) \leq F_1(t)$ or equivalently, $S_0(t) \geq S_1(t)$.

For the case of a fully effective intervention that completely eliminates the exposure at time zero among all those exposed, the obvious extension of the attributable risk in the survival context is the attributable risk function

$$AR(t) = \frac{F(t) - F_0(t)}{F(t)} = \frac{S_0(t) - S(t)}{1 - S(t)} = \frac{\pi[S_0(t) - S_1(t)]}{\pi[S_0(t) - S_1(t)] + 1 - S_0(t)} \quad (2)$$

If we fix a particular time point, $t = t^*$, then we obtain equation (1) with $P(D) = F(t^*)$. The attributable risk function is interpreted as the proportion of disease that would be prevented at time t by a fully effective intervention, relative to the cumulative incidence proportion at time t with no intervention. Panel (Ia) of Figure 1 depicts the three survival distributions, as well as the numerator and denominator of equation (2).

Clearly, $AR(t) \leq 1$, and $S_0(t) \geq S_1(t)$ is equivalent to $AR(t) \geq 0$; equation (2) also shows that $AR(\infty) = \lim_{t \rightarrow \infty} AR(t) = 0$, and for $t \rightarrow 0^+$ we have

$$AR(0^+) = \lim_{t \rightarrow 0^+} 1 - \frac{1}{\pi \frac{f_1(t)}{f_0(t)} + 1 - \pi}$$

(assuming $f_0(t) > 0$ for $0 < t < \varepsilon$) where $f_0(t)$ and $f_1(t)$ are the corresponding density functions. The assumption $S_0(t) \geq S_1(t)$ implies $1 \leq \lim_{t \rightarrow 0^+} f_1(t)/f_0(t)$, so that $AR(0^+) < 1$ unless $\lim_{t \rightarrow 0^+} f_1(t)/f_0(t) = \infty$; in particular, $AR(0^+) = 0$ when $\lim_{t \rightarrow 0^+} f_1(t)/f_0(t) = 1$.

Because of its limiting behavior, $AR(t)$ can only be monotone decreasing, and only if $AR(0^+) > 0$; examples show that even in this case, $AR(t)$ need not be monotone. We note that (2) will be decreasing whenever

$$\frac{f_1(t)}{F_1(t)} \leq \frac{f_0(t)}{F_0(t)}$$

or equivalently, when the odds ratio for failure by time t exceeds the hazard ratio

$$OR_F(t) = \frac{F_1(t)/S_1(t)}{F_0(t)/S_0(t)} \geq \frac{h_1(t)}{h_0(t)}$$

2.2. Hazard-based alternatives

Chen *et al.* [4] and Samuelsen and Eide [5] considered a measure of attributable risk in which the estimate of disease risk is based on the hazard. The overall population hazard function is

$$h(t) = \frac{\pi f_1(t) + (1 - \pi)f_0(t)}{\pi S_1(t) + (1 - \pi)S_0(t)} = \pi(t)h_1(t) + [1 - \pi(t)]h_0(t)$$

where

$$\pi(t) = \frac{\pi S_1(t)}{\pi S_1(t) + (1 - \pi)S_0(t)} = \frac{\pi S_1(t)}{S(t)}$$

is the proportion exposed at time $t \geq 0$. We have $\pi(0) = \pi$, and under the assumption $h_1(t) \geq h_0(t)$, $\pi(t)$ is monotone decreasing with time; the exposed are subject to a greater hazard and are therefore more rapidly depleted from the population. The limiting value of $\pi(t)$ depends on the ratio $S_1(t)/S_0(t)$, which can also be interpreted as the odds ratio for exposure at time t , $S_1(t)/S_0(t) = [(1 - \pi)/\pi]\pi(t)/[1 - \pi(t)] = OR_e(t)$; thus $OR_e(\infty) = 0$ is equivalent to $\pi(\infty) = 0$.

Assuming that the intervention is fully effective, the hazard-based attributable risk function, the attributable hazard, is

$$AR_h(t) = 1 - \frac{h_0(t)}{h(t)} = \frac{\pi(t)[h_1(t) - h_0(t)]}{\pi(t)[h_1(t) - h_0(t)] + h_0(t)} \quad (3)$$

This measure can be interpreted as the approximate proportion of events that are prevented in a small interval of time $[t, t + \Delta)$. It follows from (3) that $h_1(t) \geq h_0(t)$ is required in order to have $AR_h(t) \geq 0$. The limiting behavior of (3) is governed by the ratio of the corresponding hazard functions rather than the ratio of the densities. Under the assumption $h_1(t) \geq h_0(t)$, it can easily be shown that $0 \leq AR_h(0^+) = AR(0^+) \leq 1$ and $AR_h(\infty) = 0 = AR(\infty)$. Chen *et al.* [4] provided estimation procedures for (3) and (2) based on the Cox proportional hazards model.

Alternatively, Silverberg *et al.* [6] and Samuelsen and Eide [5] used the original proportion exposed, $\pi = \pi(0)$ to weight the difference between the two hazard functions in (3). That is, analogous to the overall survival function, define the combined hazard as $h^\pi(t) = \pi h_1(t) + (1 - \pi)h_0(t)$; the alternative hazard-based measure uses the combined, mixture hazard instead of the population hazard

$$AR_h^\pi(t) = 1 - \frac{h_0(t)}{h^\pi(t)} = \frac{\pi[h_1(t) - h_0(t)]}{\pi h_1(t) + (1 - \pi)h_0(t)} = \frac{\pi[h_1(t) - h_0(t)]}{\pi[h_1(t) - h_0(t)] + h_0(t)}$$

However, the survival function corresponding to $h^\pi(t)$ is $S^\pi(t) = S_1^\pi(t)S_0^{1-\pi}(t) \leq S(t)$, which under-estimates the overall survival function in the actual population; thus, we believe that this approach does not provide a useful measure of public health risk.

3. ATTRIBUTION IN THE SURVIVAL CONTEXT

3.1. Attributable survival

If the measure of disease is the cumulative failure rate, then the obvious extension of attributable risk is the attributable risk function. In the survival context, however, an alternative measure of the public health significance of an intervention is the proportion of the resulting survival, after the intervention is carried out, that is due to the intervention. In particular, if prior to the intervention the population survival function is $S(t)$, and after the intervention the population survival function becomes $S_0(t) = S(t) + [S_0(t) - S(t)]$, then the part of $S_0(t)$ resulting from the intervention $[S_0(t) - S(t)]$ is the attributable portion. In other words, the attributable survival is the proportion of survivors with the intervention who would have experienced the event had the intervention not been administered. Specifically, we define the attributable survival function as

$$AS(t) = \frac{S_0(t) - S(t)}{S_0(t)} = \pi \frac{S_0(t) - S_1(t)}{S_0(t)} = \pi \left[1 - \frac{S_1(t)}{S_0(t)} \right] \quad (4)$$

Panel (Ib) of Figure 1 provides a graphical depiction of (4), showing that the numerator is less than the denominator, resulting in a measure between zero and one. The attributable survival is related to but distinct from the preventable fraction, which corresponds to $PF(t) = [S(t) - S_1(t)]/[1 - S_1(t)] = (1 - \pi)[S_0(t) - S_1(t)]/[1 - S_1(t)]$. It is also in contrast to an alternative measure using $S(t)$ as the denominator (i.e. $AS(t)/[1 - AS(t)]$), which has the properties of an odds instead of a proportion, making its interpretation as an attributable fraction difficult. The attributable survival does bear a functional if not an exact conceptual relationship to the susceptible fraction discussed by Khoury *et al.* [7], whose definition, under certain independence assumptions about the relationship between exposure and the underlying disease process, corresponds to $AS(t)/\pi$, so that the definition is independent of the proportion exposed.

Clearly, $AS(0) = 0$ and $0 \leq AS(\infty) \leq \pi$, depending on $1 \geq OR_e(\infty) = \lim_{t \rightarrow \infty} S_1(t)/S_0(t) = \lim_{t \rightarrow \infty} f_1(t)/f_0(t) \geq 0$, or equivalently on the limiting odds of exposure $\pi(t)/[1 - \pi(t)] = \pi S_1(t)/[(1 - \pi)S_0(t)]$, so that $AS(\infty) = \pi[1 - OR_e(\infty)] = \pi - (1 - \pi)\pi(\infty)/[1 - \pi(\infty)]$. We expect that the effect of exposure would typically be such that $\pi(\infty) = 0$, in which case $AS(\infty) = \pi$; the limiting attributable survival is the original proportion exposed. That is, if the intervention entirely eliminates the exposure of the π per cent of the population that was originally exposed, then π per cent of the resulting survival in the population over the entire time span is due to such an intervention. Under the additional assumption $h_1(t) \geq h_0(t)$, (4) is monotone increasing since $\partial AS(t)/\partial t = \pi[h_1(t) - h_0(t)]S_1(t)/S_0(t)$.

The attributable risk function (2) is the product of the survival odds and the attributable survival odds

$$AR(t) = \frac{S_0(t) - S(t)}{1 - S(t)} = \frac{S(t)}{1 - S(t)} \frac{AS(t)}{1 - AS(t)}$$

Thus, initially $AR(t) > AS(t)$, except possibly for $AR(0^+) = 0 = AS(0)$, until the unique $t^* > 0$ when $S_0(t^*) = 1 - S(t^*)$, after which $AR(t) < AS(t)$.

3.2. Attributable survival time

The attributable survival represents the additional proportion of individuals in the population who survive to a given time if the exposure is eliminated, but it does not account for the actual survival time. To provide a measure of the gain in survival time resulting from an intervention, we can use the area under the survival curve, $E_i(t) = \int_0^t S_i(u) du$. Changing the order of integration (or integrating by parts) shows that $E_i(t)$ can be interpreted as the expected survival time at time t . Specifically, letting T_1 and T_0 denote the random event times in the exposed and unexposed populations,

$$E_i(t) = \int_0^t S_i(u) du = \int_0^t u f_i(u) du + t S_i(t) = F_i(t) E(T_i | T_i \leq t) + [1 - F_i(t)] t$$

Thus, $E_i(t)$ is a weighted average, according to the probability of having the event before t , $[F_i(t)]$ of the expected value before t $[E(T_i | T_i \leq t)]$ and t itself. The expected survival to time t in the entire population is $E(t) = \pi E_1(t) + (1 - \pi) E_0(t)$.

The attributable survival time is defined as the ratio of the change in expected survival time resulting from the intervention to that achieved by the intervention,

$$AST(t) = \frac{E_0(t) - E(t)}{E_0(t)} = \pi \left[1 - \frac{E_1(t)}{E_0(t)} \right] = \pi \left[1 - \frac{F_1(t) E(T_1 | T_1 \leq t) + [1 - F_1(t)] t}{F_0(t) E(T_0 | T_0 \leq t) + [1 - F_0(t)] t} \right] \quad (5)$$

As with the attributable survival we have $AST(0^+) = 0$, and

$$AST(\infty) = \pi \left[1 - \frac{E(T_1)}{E(T_0)} \right] = \pi \left[\frac{E(T_0) - E(T_1)}{E(T_0)} \right]$$

Thus, for a fully effective intervention, $AST(\infty)$ represents the average gain in survival time relative to that in the unexposed population (the distribution resulting from the intervention),

times the proportion of the population in which this gain was achieved; the scale in this case is the survival time rather than the survival rate.

The attributable survival time (5) clearly also has an interpretation in terms of areas under the survival curves

$$AST(t) = \frac{E_0(t) - E(t)}{E_0(t)} = \frac{\int_0^t S_0(u) - S(u) du}{\int_0^t S_0(u) du}$$

Panel (Ic) of Figure 1 shows a graphical representation of this relationship, with the area shaded with lines representing the numerator and the fully shaded area the denominator. We have $\partial AST(t)/\partial t > 0$ provided $AST(t) < AS(t)$. Assuming that $AS(t)$ is increasing, $AST(0^+) = 0$ implies that $AST(t) < AS(t)$, so that $AST(t)$ is also increasing, with $AST(\infty) < AS(\infty) = \pi$.

4. PARTIALLY EFFECTIVE INTERVENTIONS AT DISCRETE TIMES

4.1. A partially effective intervention occurring after time zero

In the previous section we introduced the attributable survival (4) and attributable survival time (5) for the simple case of a fully effective intervention which effectively eliminates exposure at time zero. We now extend these concepts to the case of an intervention that is only partly effective, and that does not necessarily occur at time zero. That is, at time $\tau \geq 0$ after the beginning of follow-up, we assume that the exposure is eliminated for only a proportion of those remaining exposed. We also allow the possibility that at the same time, a proportion of the unexposed become exposed. Greater generality is clearly possible, but to simplify the discussion we consider the following basic model. Given the initial proportion exposed, $0 < \pi < 1$, we assume that at time $\tau \geq 0$, exposure ends for a proportion p_{10} ($0 < p_{10} \leq 1$) of the $\pi S_1(\tau)$ surviving exposed, and simultaneously a proportion p_{01} ($0 < p_{01} \leq 1$) of the $(1 - \pi)S_0(t)$ surviving unexposed become exposed. A fully effective intervention corresponds to $\tau = 0$, $p_{10} = 1$ and $p_{01} = 0$.

For the group no longer exposed, the original hazard is $h_1(t)$ for $t < \tau$ and then $h_{10}(t)$ for $t \geq \tau$, whereas for the newly exposed group the hazard is $h_0(t)$ for $t < \tau$ and $h_{01}(t)$ for $t \geq \tau$. An example of an abrupt change in the hazard, where previous exposure has no residual effect, is $h_{10}(t) = h_0(t)$, and an example of a gradual drift is $h_{10}(t) = (\tau/t)h_1(t) + [1 - (\tau/t)]h_0(t)$. In general for $t \geq \tau$ we would expect that $h_0(t) \leq h_{10}(t)$, $h_{01}(t) \leq h_1(t)$. To allow the possibility that those who remain exposed are not the representative of the original exposed group, we may assume that their hazard becomes $h_{11}(t)$ for $t \geq \tau$, and similarly, for those who remain unexposed the hazard is $h_{00}(t)$ for $t \geq \tau$. For simplicity we will assume $h_{10}(t) = h_0(t)$ and $h_{01}(t) = h_1(t)$, and correspondingly, $h_{11}(t) = h_1(t)$ and $h_{00}(t) = h_0(t)$, so that the survival process has no memory of exposure prior to the intervention, and the groups for whom exposure status changes (does not change) are selected on a representative basis; these assumptions are somewhat simplistic but serve as a good starting point for our discussion.

The resulting survival functions treat these groups as late entries at the change point, corresponding to the change in the hazard. Using this formulation we can write the overall survival function under a partially effective intervention at $\tau \geq 0$ with $\mathbf{p} = (p_{10}, p_{01})$ in terms of the conditional survival functions $S_i(t|\tau) = S_i(t)/S_i(\tau)$ for $i = 0, 1$ and $t \geq \tau$ as follows. For $0 \leq t \leq \tau$ we have $S(t; \tau, \mathbf{p}) = S(t)$, and for $\tau < t$,

$$\begin{aligned} S(t; \tau, \mathbf{p}) &= (1 - p_{10})\pi S_1(t) + p_{10}\pi S_1(\tau)S_0(t)/S_0(\tau) + (1 - p_{01})(1 - \pi)S_0(t) + p_{01}(1 - \pi)S_0(\tau)S_1(t)/S_1(\tau) \\ &= S(t) + [p_{10}\pi S_1(\tau) - p_{01}(1 - \pi)S_0(\tau)][S_0(t|\tau) - S_1(t|\tau)] \end{aligned}$$

Assuming $h_1(t) \geq h_0(t)$ we clearly have $S_1(t) \leq S(t; \tau, \mathbf{p}) \leq S_0(t)$; furthermore, $S_0(t|\tau) \geq S_1(t|\tau)$, and the intervention will result in improved survival, $S(t; \tau, \mathbf{p}) \geq S(t)$ for $\tau < t$ if and only if

$$\frac{p_{10}}{p_{01}} \geq \frac{(1 - \pi)S_0(\tau)}{\pi S_1(\tau)}$$

That is, survival will improve as a result of the intervention if the relative effect of the intervention exceeds the odds of being unexposed, $p_{10}/p_{01} \geq [1 - \pi(\tau)]/\pi(\tau)$ at time $\tau \geq 0$; an equivalent condition is that the odds of being unexposed after the intervention are greater than the odds of being unexposed prior to the intervention.

We can reduce this model to the simpler case where none of the unexposed become exposed, $p_{10} = p$ and $p_{01} = 0$ by defining

$$p = \frac{p_{10}\pi S_1(\tau) - p_{01}(1 - \pi)S_0(\tau)}{\pi S_1(\tau)}$$

The value of the parameter p will be positive if the intervention produces an improvement in survival. For simplicity, we will assume $p_{10} = p$ and $p_{01} = 0$, with $0 < p \leq 1$, so that, with a slight change of notation, we have, for $t \geq \tau$

$$\begin{aligned} S(t; \tau, p) &= S(t) + p\pi S_1(\tau)[S_0(t|\tau) - S_1(t|\tau)] \\ &= (1 - p)\pi S_1(\tau)S_1(t|\tau) + [p\pi S_1(\tau) + (1 - \pi)S_0(\tau)]S_0(t|\tau) \end{aligned}$$

Thus, $S(t; \tau, p)$ can be represented as a mixture of conditional survival functions, where the mixing proportions sum to $S(\tau) = \pi S_1(\tau) + (1 - \pi)S_0(\tau)$, the proportion remaining at risk at time τ . The right-hand panels of Figure 1 depict the example of an intervention at time $\tau = 2$ that is completely effective ($p = 1$), where $S^*(t) = S(t; 2, 1)$. The fully effective intervention discussed earlier corresponds to $S(t; 0, 1) = S_0(t)$.

4.2. Attributable risk

We can now define the generalization of the attributable risk function (2). This is

$$\begin{aligned} \text{AR}(t; \tau, p) &= 0 \quad t \leq \tau \\ &= 1 - \frac{1 - S(t; \tau, p)}{1 - S(t)} = \frac{p\pi S_1(\tau)[S_0(t|\tau) - S_1(t|\tau)]}{\pi[S_0(t) - S_1(t)] + 1 - S_0(t)} \quad t > \tau \\ &= \frac{p\pi[\text{OR}_e(\tau)S_0(t) - S_1(t)]}{\pi[S_0(t) - S_1(t)] + 1 - S_0(t)} \quad t > \tau \end{aligned} \quad (6)$$

where for convenience we write $\text{OR}_e(\tau) = S_1(\tau)/S_0(\tau) \leq 1$. The definition is represented graphically in Panel (IIa) of Figure 1 for the case $\tau = 2$ and $p = 1$. This extension was briefly considered by Samuelsen and Eide [5, Section 3.2], who also discussed the corresponding extension based on the hazard, $\text{AR}_h(t)$; the latter has the interesting property of having a jump discontinuity at time τ due to the sudden change in the hazard at time τ among the exposed who become unexposed. The definition is similar in spirit to the generalized attributable risk discussed by Drescher and Becher [8]; see also Cox [9]. The original definition (2) involves a comparison of disease risk in the overall population with that in the unexposed group, the distribution resulting from a fully effective intervention; the generalization (6) is to allow a partially effective intervention, in particular one that has no effect before time τ . An interesting special case is provided by a population with everyone initially exposed ($\pi = 1$), and an intervention that is partially effective at time $\tau = 0$,

removing a proportion $1 - p$ of the exposure. The attributable risk in this case corresponds to the preventable fraction discussed above, with a proportion p exposed, $AR(t; 0, 1 - p) = (1 - p)[S_0(t) - S_1(t)]/[1 - S_1(t)]$.

We again have $AR(\infty; \tau, p) = 0$, so that $AR(t; \tau, p)$ cannot be monotone, except in the case of a fully effective intervention, $AR(t; 0, 1) = AR(t)$. Clearly, for each $t > \tau$, $AR(t; \tau, p)$ increases as p approaches one. The limit is the special case that exposure is eliminated ($p = 1$), where we obtain a simpler expression for $\tau \leq t$.

$$AR(t; \tau, 1) = \frac{\pi[OR_e(\tau)S_0(t) - S_1(t)]}{\pi[S_0(t) - S_1(t)] + 1 - S_0(t)} < \frac{\pi[S_0(t) - S_1(t)]}{\pi[S_0(t) - S_1(t)] + 1 - S_0(t)} = AR(t)$$

In this case, as $\tau \searrow 0 (OR_e(\tau) \nearrow 1)$, we have $AR(t; \tau, 1) \nearrow AR(t)$.

4.3. Attributable survival

The attributable survival (4) is the ratio of the change in survival resulting from the intervention to the survival achieved by the intervention, which for the case of a partially effective intervention at time τ is $S(t, \tau, p)$ instead of $S_0(t)$. The attributable survival is therefore $AS(t; \tau, p) = 0$ for $t \leq \tau$, and for $t > \tau$,

$$\begin{aligned} AS(t; \tau, p) &= \frac{S(t; \tau, p) - S(t)}{S(t; \tau, p)} \\ &= \frac{p\pi S_1(\tau)[S_0(t|\tau) - S_1(t|\tau)]}{(1-p)\pi S_1(\tau)S_1(t|\tau) + [p\pi S_1(\tau) + (1-p)S_0(\tau)]S_0(t|\tau)} \\ &= \frac{p\pi[S_1(\tau)S_0(t) - S_0(\tau)S_1(t)]}{(1-p)\pi S_0(\tau)S_1(t) + [p\pi S_1(\tau) + (1-p)S_0(\tau)]S_0(t)} \end{aligned} \quad (7)$$

As above, the denominator of (7) is a mixture of conditional survival functions, with weights summing to $S(\tau)$. For the case $\tau = 2$ and $p = 1$, the numerator and denominator of (7) are shown in Panel (IIb) of Figure 1. As a special case we have $AS(t; 0, 1) = AS(t)$ in (4).

The limit $AS(\infty; \tau, p)$ is again determined by $\pi(t)$, the proportion exposed; in particular, under the assumption $\pi(\infty) = 0$,

$$AS(\infty; \tau, p) = \frac{p\pi S_1(\tau)}{p\pi S_1(\tau) + (1 - \pi)S_0(\tau)} < \pi = AS(\infty)$$

This represents the survival at time τ for the group whose exposure is eliminated by the intervention (at time τ), divided by the total unexposed at time τ . For the case $p = 1$, this total is simply $S(\tau)$, and the limit is $AS(\infty; \tau, 1) = \pi(\tau)$, the proportion exposed at time τ . For $\tau = 0$, we have $AS(\infty; 0, p) = p\pi/(p\pi + 1 - \pi)$, and $AS(\infty; 0, 1) = \pi$. These limiting results actually suggest an alternative definition of the attributable survival, in which we divide by $S(t; \tau, 1)$ instead of $S(t; \tau, p)$ in (7). This alternative definition would have the property that $AS(\infty; 0, p) = p\pi$. However, for a number of reasons, including both simplicity and interpretability, we prefer our original approach.

As with the attributable survival (4), it is not difficult to show that under the assumption $h_1(t) \geq h_0(t)$, we have $AS(t; \tau, p) \nearrow AS(\infty; \tau, p)$. For fixed t , $AS(t; \tau, p)$ is increasing as $p \nearrow 1$; in the limiting case ($p = 1$), we again have a simplification for $t > \tau$.

$$AS(t; \tau, 1) = \pi(\tau) \left[1 - \frac{S_1(t|\tau)}{S_0(t|\tau)} \right] < \pi \left[1 - \frac{S_1(t)}{S_0(t)} \right] = AS(t)$$

In this case we have for fixed t that $AS(t; \tau, 1) \nearrow AS(t)$ as $\tau \searrow 0$ ($OR_e(\tau) \nearrow 1$). Thus the more the exposure that is eliminated by the intervention and the earlier it occurs, the larger the attributable survival.

4.4. Attributable survival time

To extend the attributable survival time (5) to the case of a partially effective intervention, we must define the expected survival time for $t > \tau$,

$$\begin{aligned} E(t; \tau, p) &= \int_0^t S(u; \tau, p) du = \int_0^t S(u) du + p\pi S_1(\tau) \int_\tau^t S_0(u|\tau) - S_1(u|\tau) du \\ &= E(t) + p\pi S_1(\tau) [E_0(t|\tau) - E_1(t|\tau)] \\ &= E(\tau) + (1 - p)\pi S_1(\tau) E_1(t|\tau) + [p\pi S_1(\tau) + (1 - \pi)S_0(\tau)] E_0(t|\tau) \end{aligned}$$

where $E_i(t|\tau) = \int_\tau^t S_i(u|\tau) du = [E_i(t) - E_i(\tau)]/S_i(\tau)$. The attributable survival time is the proportionate gain in the expected survival time up to time t , represented in Panel (IIc) of Figure 1 for the case $\tau = 2$ and $p = 1$. Specifically, $AST(t; \tau, p) = 0$ for $t \leq \tau$, and for $t > \tau$,

$$\begin{aligned} AST(t; \tau, p) &= 1 - \frac{E(t)}{E(t; \tau, p)} \\ &= \frac{p\pi S_1(\tau) [E_0(t|\tau) - E_1(t|\tau)]}{E(\tau) + (1 - p)\pi S_1(\tau) E_1(t|\tau) + [p\pi S_1(\tau) + (1 - \pi)S_0(\tau)] E_0(t|\tau)} \\ &= \frac{p\pi [S_0(\tau) E_1(\tau) - S_1(\tau) E_0(\tau) + S_1(\tau) E_0(t) - S_0(\tau) E_1(t)]}{p\pi [S_0(\tau) E_1(\tau) - S_1(\tau) E_0(\tau) + (1 - p)S_0(\tau) E_1(t) + [p\pi S_1(\tau) + (1 - \pi)S_0(\tau)] E_0(t)]} \end{aligned} \quad (8)$$

The denominator of the second expression is the sum of $E(\tau)$ and a mixture with the same weights as the attributable survival, summing to $S(\tau)$. For a fully effective intervention we have $AST(t; 0, 1) = AST(t)$.

As $t \rightarrow \infty$, we have

$$AST(\infty; \tau, p) = \frac{p\pi S_1(\tau) [E(T_0|\tau) - E(T_1|\tau)]}{E(\tau) + (1 - p)\pi S_1(\tau) E(T_1|\tau) + [p\pi S_1(\tau) + (1 - \pi)S_0(\tau)] E(T_0|\tau)}$$

where $E(T_i|\tau) = E_i(\infty|\tau) = [E(T_i) - E_i(\tau)]/S_i(\tau)$ is the mean residual life at time τ . Similar to (5), the limit has a simple interpretation in terms of the expected survival time; the numerator is the proportionate expected gain in residual lifetime among those whose exposure is eliminated, and the denominator is the expected total survival time under the intervention. Since $AS(t; \tau, p)$ is increasing for $0 < p \leq 1$, it can be shown by an argument similar to that for the attributable survival time (5) that $AST(t; \tau, p) \leq AS(t; \tau, p)$ is also increasing. For fixed $t > \tau$, as $p \nearrow 1$, $AST(t; \tau, p)$ increases to $AST(t; \tau, 1)$. In addition, for the case $p = 1$ we have that $AST(t; \tau, 1) \nearrow AST(t; 0, 1) = AS(t)$ as $\tau \searrow 0$, in particular $AST(t; \tau, 1) \leq AS(t)$. As was the case for the attributable survival, the more the exposure that is eliminated by the intervention and the earlier it occurs, the larger the attributable survival time (8).

5. AN EXAMPLE AND AN APPLICATION

5.1. An exponential example

A simple example is provided by the case of two exponential distributions. Suppose $S_0(t) = e^{-\lambda_0 t}$ and $S_1(t) = e^{-\lambda_1 t}$, with $\lambda_1 > \lambda_0$. In this case $S(t) = \pi e^{-\lambda_1 t} + (1 - \pi) e^{-\lambda_0 t}$, $E_i(t) = (1 - e^{-\lambda_i t})/\lambda_i$, and for $t > \tau$, $S(t; \tau, p) = S(t) + p\pi[e^{-(\lambda_1 - \lambda_0)\tau} e^{-\lambda_0 t} - e^{-\lambda_1 t}]$, $E_i(t|\tau) = (1 - e^{-\lambda_i(t-\tau)})/\lambda_i$, and of course $E(T_i|\tau) = 1/\lambda_i$. We also have $\pi(\infty) = 0$ for this example. Table I summarizes the four different measures of attribution. Graphs of these functions for $(\lambda_1, \lambda_0, \pi) = (1.5, 0.5, 0.6)$, and both a fully effective $(\tau, p) = (0, 1)$ and partially effective $(\tau, p) = (1, 0.8)$ intervention, are shown in Figure 2. Both $AR(t)$ and $AR_h(t)$ are strictly decreasing from their common left-hand limit $AR(0^+) = 0.545$. In this case, $AR_h(t)$ is a reasonable approximation to $AR(t)$; see also Figure 2 of Chen *et al.* [4]. Both $AS(t; \tau, p)$ and $AST(t; \tau, p)$ are increasing, and $AST(t; \tau, p) < AS(t; \tau, p)$. We have $AS(\infty) = \pi = 0.6$, and $AST(\infty) = 0.6(1.5 - 0.5)/1.5 = 0.4$. Similarly, $AS(\infty; 1, 0.8) = 0.306$, and $AST(\infty; 1, 0.8) = 0.106$.

5.2. An application: Study design and methods

In the absence of treatment, individuals who become infected with HIV are at risk of AIDS and subsequent death. Treatments for HIV have evolved from a period of no available therapy (prior to 1987) to combinations of three or more drugs (after 1995), collectively known as HAART (DHHS/Henry J. Kaiser Family Foundation Panel, 2006). Since the evolution of HIV therapy followed a definite pattern over time, it is possible to define sequential calendar periods corresponding to distinct therapeutic eras. Cox *et al.* [10], distinguished four such periods, the first an initial period of no or only monotherapy (July 1984–December 1989), followed by two intermediate periods, and the final period the (short to moderate-term stable) era of HAART (July 1998 – December 2003). To illustrate the attributable survival and compare it with the conventional attributable risk function, we chose the first and last of the four periods, corresponding to essentially no effective treatment (exposed) vs highly effective HAART therapy (unexposed), the intervention that we wish to study. Thus, the survival function for the first period corresponds to $S_1(t)$, and that for the HAART era is $S_0(t)$. The outcome of interest in this analysis was the time from a diagnosis of clinical AIDS to death.

We based our analysis on data from the Multicenter AIDS Cohort Study (MACS), a longitudinal study of HIV-1 infection in a cohort of homosexual and bisexual men, which began in 1983 [11]. The MACS conducts semi-annual interviews, which include detailed questions about the use of antiretroviral therapy. Deaths are ascertained using both active and passive methods, including abstraction of death certificates and searches of national death registries. Schneider *et al.* [12] showed that a high percentage of participants with clinical AIDS used HAART between early 1995 and December 2003.

The analysis included a total of 786 men with follow-up after an incident diagnosis of clinical AIDS. In this study, AIDS was defined using the 1993 CDC surveillance criteria [13] based on clinical conditions (i.e. excluding the laboratory criterion of low CD4 count). For simplicity, individuals with an AIDS diagnosis in the first period who were still alive at the end of the period were treated as censored observations, and did not contribute time to the subsequent calendar periods. Individuals with a diagnosis after January 1995, when HAART therapy became widely available, were eligible for inclusion in the last (fourth) period. Those with a diagnosis before the beginning of the last period who survived until the beginning of the period were treated as late entries. For purposes of comparison we chose two values for the proportion untreated, $\pi = 0.7$ and 0.3 . To study the effects of delayed treatment for a proportion of the untreated population, we chose $\tau = 1$ year and, for comparison, $p = 1.0$ and 0.5 .

The free, downloadable R software (<http://www.r-project.org/>) was used for both parametric and nonparametric estimation of the attributable risk, attributable survival, and the attributable survival time. The three-parameter generalized gamma (GG) distribution was used for parametric estimation [10]. The analysis included likelihood ratio tests to determine whether the two-parameter Weibull and log normal models provided an adequate fit. For the attributable survival time, a numerical integration method was implemented through the cumulative summation function `cumsum()`. The programs are available upon request.

5.3. An application: results

For the first period, a GG model provided an adequate fit, with parameter estimates (SE) $\beta = 0.6737(0.0716)$, $\sigma = 0.7731(0.0679)$ and $\lambda = 1.369(0.189)$, while for the last period a Weibull ($\lambda = 1$) fit was reasonable, with parameters $\beta = 3.053(0.298)$ and $\sigma = 1.617(0.299)$. Figure 3 shows the survival curves for the two periods. Included are parametric (GG for $S_1(t)$ and Weibull for $S_0(t)$) and product limit estimates, indicating that the parametric models in this case provided a good fit to the data. The two sets of survival curves show the dramatic improvement in survival after a diagnosis of AIDS, resulting from the introduction of HAART therapy. In addition, we have included $S(t)$ for $\pi = 0.7$, and the corresponding $S^*(t) = S(t; \tau, p)$ for $\tau = 1$ and $p = 0.5$.

In Figure 4 we present parametric and in Figure 5 nonparametric examples of the attributable risk, attributable survival, and attributable survival time curves for the different combinations of the parameters. In addition, Figure 4 includes $AR_h(t)$ as an alternative to $AR(t)$. By definition data are only available for 4 years in period one, while follow up in period two extends for 8 years. For purposes of comparison the time scale in Figures 4 and 5 has been set at 6 years, and the parametric curves projected beyond the actual data. The attributable risk function starts at zero, increases to a maximum, and then begins to decline toward zero. The attributable hazard behaves similarly, but in this case does not follow the attributable risk very closely. This example indicates that the attributable hazard can be quite different from the attributable risk. The attributable survival function increases from zero, and by 5 years most of the attributable survival has been realized. Initially $AR(t) > AS(t)$ for $t > 0$, and the two curves cross exactly once. We also show $AS(t; \tau, p)$ curves for $\tau = 1$ and $p = 1.0$ and 0.5 . The first of these curves looks similar to the original attributable survival function. The curves for the attributable survival time have a similar shape, but reflect the effect of averaging. As the fit of the parametric models is quite good, it is no surprise that the curves on Figures 4 and 5 are similar, although of course this will not always be the case.

6. DISCUSSION

We have considered the extension of the attributable risk to the attributable risk function in the context of survival analysis, and have proposed two new measures, the attributable survival and attributable survival time. The attributable survival function tracks the gain in survival rather than the decrease in risk, and the attributable survival time provides a cumulative measure, leading to an interpretation based on the relative gain in survival time rather than survival rate. We believe that these new measures are appropriate and useful in the survival context; of the two, the attributable survival is easier to compute and perhaps more likely to be useful in practice.

Under the assumption $h_1(t) \geq h_0(t)$, both $AS(t)$ and $AST(t)$ are increasing, so that the benefit of a treatment or intervention accumulates over time. In contrast, $AR(t)$ can initially take any value between zero and one depending on the limiting properties of the two density functions, and its subsequent behavior is then strongly influenced by this initial value. Another undesirable property of the attributable risk function is that the risk attributable to

any intervention is eventually zero, a property that reflects the behavior of the two survival functions more than the intervention.

All of these measures can be computed with standard statistical software using either a parametric or nonparametric approach, as illustrated by the application. When nonparametric methods are used and the longest observed time is censored, both attributable survival [AS(t) and AST(t)] and attributable risk [AR(t)] can only be computed up to that time. An advantage of parametric methods is the ability to obtain all of these measures for arbitrary $t \geq 0$. Caution should be used, however, since it is generally not recommended to extrapolate results beyond the range of the data.

As part of the inference it is frequently useful to also calculate a standard error. For parametric models, approximate standard errors for the individual survival functions can be obtained using the delta method, and for the nonparametric approach Greenwood's formula can be used. In either case an approximate standard error for the attributable survival (or its logarithm) can then be computed using the delta method. Similar computations are discussed and illustrated by Cox *et al.* [10]. An alternative approach is to use the bootstrap; additional smoothing of bootstrap confidence intervals at individual values of time may be desired to produce smooth looking bands. Simultaneous confidence bands can also be produced using either parametric [14] or nonparametric approaches [15]. A similar approach can in theory also be used for the attributable survival time, although to use the delta method one must integrate the derivatives of the survival functions with respect to the parameters.

In addition to considering attributable survival for the case of populations that are either always exposed or unexposed (a completely effective intervention), we have discussed the generalization to the situation where exposure changes with time. Our discussion was limited to the case of a single time point, and to interventions for which those who remain exposed are representative of the originally exposed, while those who become unexposed abruptly change to the same hazard as the originally unexposed, and similarly for the unexposed. These conditions may not hold in observational studies where the intervention is not randomized, or in situations where previous exposure has a lasting effect. As we have indicated, the measures can be extended by allowing the hazard functions for those who do not change their exposure status to be different from the original hazards. In addition they can also be extended to the case of more than one time point at which the intervention is administered. The details are increasingly cumbersome, but there are no methodological limitations.

A related generalization is to allow several levels of exposure as well as adjustment for covariates [5,9]. The simplest framework is to partition the population into K strata, defined by Z_K . The conditional survival function is $S_k(t) = S(t|Z_K = k)$, and we let $\pi_k = P(Z_K = k)$. The overall survival function is then $S(t) = \sum_k \pi_k S_k(t)$. We now assume that the intervention results in an alternative distribution $\pi_k^* = P^*(Z_K = k)$; the resulting survival function is then

$S^*(t) = \sum_k \pi_k^* S_k(t)$, and the adjusted attributable survival function is

$$AS(t) = \frac{S^*(t) - S(t)}{S^*(t)}$$

The generalizations of the attributable survival time and attributable risk are also straightforward.

Acknowledgments

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at The Johns Hopkins University Bloomberg School of Public Health (Joseph B. Margolick, Lisa Jacobson), Howard Brown Health Center and Northwestern University Medical School (John Phair), University of California, Los Angeles (Roger Detels), and University of Pittsburgh (Charles Rinaldo).

Studies were approved by the Committees of Human Research of participating institutions. The MACS web site is located at <http://statepi.jhsph.edu>.

Contract/grant sponsor: National Institute of Allergy and Infectious Diseases; contract/grant numbers: UO1-AI-35042, UO1-AI-35043, UO1-AI-35039, UO1-AI-35040, UO1-AI-35041

Contract/grant sponsor: National Center for Research Resources; contract/grant number: MO1-RR-00052

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Figure 1.

Definitions of attributable risk (Ia) and (IIa), attributable survival (Ib) and (IIb) and attributable survival time (Ic) and (IIc) in the survival context. (Ia–Ic) correspond to a fully effective intervention, and (IIa–IIc) correspond to a generalization allowing a partially effective, time-varying intervention. In this example, $\tau = 2$, as indicated by the arrow, $p = 1$ and $S^*(t) = S(t; 2, 1)$.

Figure 2.

Graphs of $AR(t, \tau, p)$, $AR_h(t, \tau, p)$, $AS(t, \tau, p)$ and $AST(t, \tau, p)$ for exponential distributions with $(\lambda_1, \lambda_0, \pi) = (1.5, 0.5, 0.6)$ and both a fully effective $(\tau, p) = (0, 1)$ and partially effective $(\tau, p) = (1, 0.8)$ intervention.

Figure 3.

Survival curves for calendar periods representing treated and untreated subjects with AIDS in the Multicenter AIDS Cohort Study (MACS) study. Included are parametric generalized gamma curves for untreated [$S_1(t)$] and Weibull for treated [$S_0(t)$] periods, as well as the corresponding Kaplan–Meier curves. $S(t)$ for $\pi = 0.7$ and $S^*(t) = S(t; 1, 0.5)$ are also shown.

Figure 4.

Illustrations of the attributable risk, the attributable hazard, attributable survival and attributable survival time curves for different combinations of τ and p for the MACS data using generalized gamma and Weibull distributions for untreated and treated periods, respectively.

Figure 5. Illustrations of the attributable risk, attributable survival and attributable survival time curves for different combinations of τ and p for the MACS data using the Kaplan–Meier estimates.

Table I

Attributable risk, survival and survival time functions for the case of two exponential distributions with parameters $\lambda_1 > \lambda_0$.

Attribution	Function ($t \geq \tau \geq 0$)	$t = 0^+$	$(0, \infty)$	$t \rightarrow \infty$
AR(t)	$\frac{\pi[1 - e^{(\lambda_0 - \lambda_1)t}]}{\pi[1 - e^{(\lambda_0 - \lambda_1)t}] + e^{\lambda_0 t} - 1}$	$0 < \frac{\pi(\lambda_1 - \lambda_0)}{\pi(\lambda_1 - \lambda_0) + \lambda_0} < 1$	Decreasing	0
AR _b (t)	$\frac{\pi(\lambda_1 - \lambda_0)}{\pi\lambda_1 + (1 - \pi)\lambda_0 e^{(\lambda_1 - \lambda_0)t}}$	AR(0^+)	Decreasing	0
AS(t)	$\pi[1 - e^{(\lambda_0 - \lambda_1)t}]$	0	Increasing	π
AST(t)	$\pi \frac{\lambda_1(1 - e^{-\lambda_0 t}) - \lambda_0(1 - e^{-\lambda_1 t})}{\lambda_1(1 - e^{-\lambda_0 t})}$	0	Increasing	$\pi \frac{\lambda_1 - \lambda_0}{\lambda_1}$
AR($t; \tau, p$)	$\frac{p\pi[e^{(\lambda_0 - \lambda_1)\tau} - e^{(\lambda_0 - \lambda_1)t}]}{\pi[1 - e^{(\lambda_0 - \lambda_1)t}] + e^{\lambda_0 t} - 1}$	AR($t; \tau, p$) = 0 ($t \leq \tau$)	Arc-shaped	0
AS($t; \tau, p$)	$\frac{p\pi[e^{-\lambda_0(t-\tau)} - e^{-\lambda_1(t-\tau)}]}{(1-p)\pi e^{-\lambda_1(t-\tau)} + [p\pi + (1-\pi)e^{(\lambda_1 - \lambda_0)\tau}]e^{-\lambda_0(t-\tau)}}$	AS($t; \tau, p$) = 0 ($t \leq \tau$)	Increasing	$\frac{p\pi e^{-\lambda_1 \tau}}{p\pi e^{-\lambda_1 \tau} + (1-\pi)e^{-\lambda_0 \tau}}$
AST($t; \tau, 1$)	$\frac{\pi(\lambda_1 - \lambda_0) + \lambda_0 e^{-\lambda_1(t-\tau)} - \lambda_1 e^{-\lambda_0(t-\tau)}}{\pi(\lambda_1 - \lambda_0) + [(1-\pi)\lambda_1 + \pi\lambda_0]e^{\lambda_1 \tau} - \lambda_1[(1-\pi)e^{\lambda_1 \tau} + \pi e^{\lambda_0 \tau}]e^{-\lambda_0 t}}$	AST($t; \tau, p$) = 0 ($t \leq \tau$)	Increasing	$\frac{\pi(\lambda_1 - \lambda_0)}{\pi(\lambda_1 - \lambda_0) + [(1-\pi)\lambda_1 + \pi\lambda_0]e^{\lambda_1 \tau}}$