Estimation of the proportion of patients who benefit from a treatment in a positive randomised trial, using a novel variance-guided equation
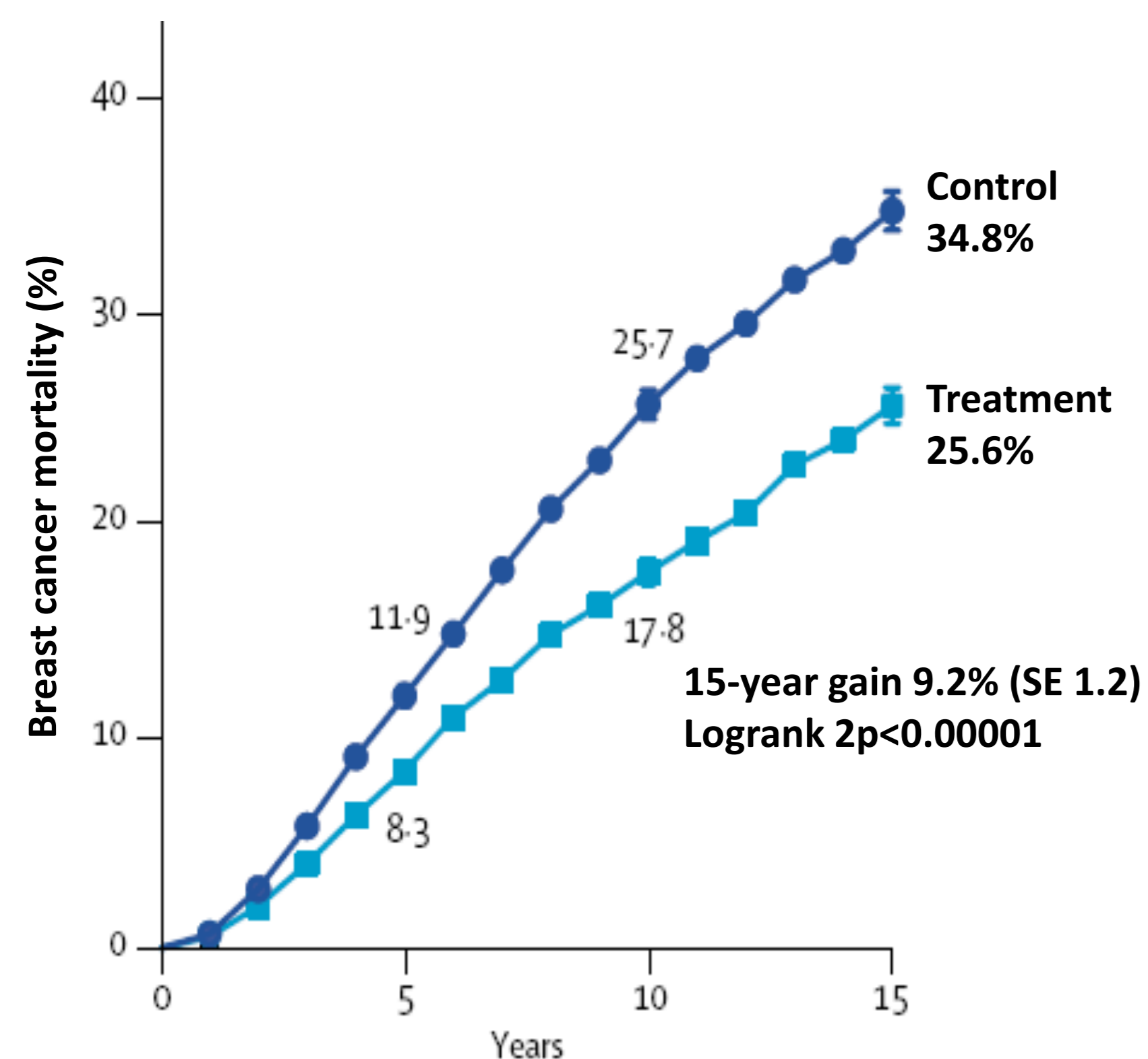
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The Problem

From the results of a positive randomised clinical trial, it cannot be ascertained whether the additional benefit is distributed to all patients or is limited to only a subgroup.

For example, from these data one can derive that there is a 9.2% reduction in mortality.
Does this mean...
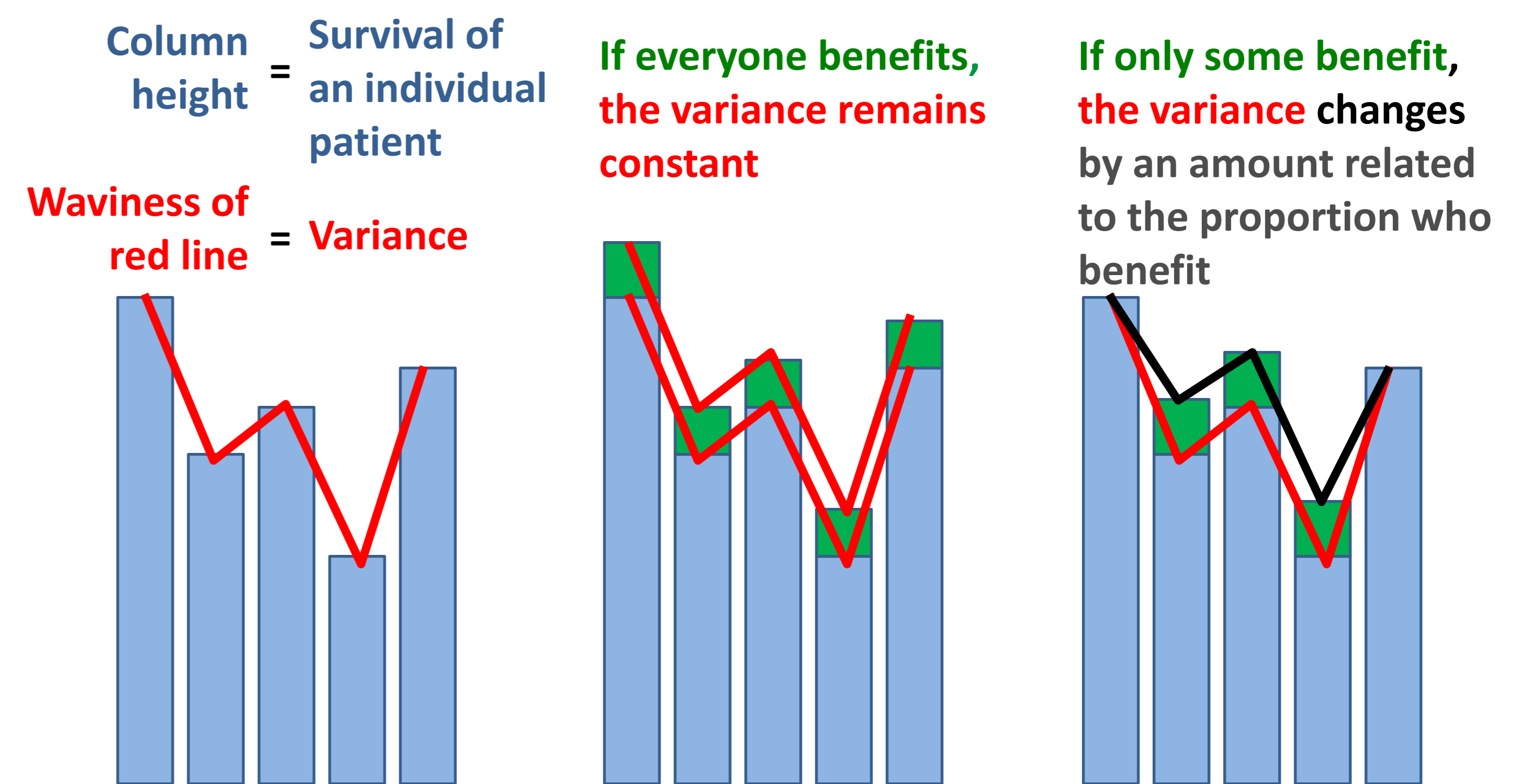• **Every patient's life span is increased by 9.2%?**
Or
• **Only 9.2% patients benefit and the other 90.8% derive no benefit?**
Or, most plausibly,
• **Only a proportion of patient's life span is increased (by >9.2%) and the other patients derive no benefit?** *If so, can this proportion be estimated?*

A New Insight

The variance in length of survival in the treated group will be same as the control group if the treatment is effective in every patient; but will be different if the treatment is effective in only a subgroup.

Column height = Survival of an individual patient

Waviness of red line = Variance

If everyone benefits, the variance remains constant

If only some benefit, the variance changes by an amount related to the proportion who benefit

The Solution

We devised a new variance-guided equation to estimate the proportion P of the patients in whom a treatment is effective:

$$P = \cfrac{1}{1 + \cfrac{S_1{}^2 - S_0{}^2}{(\mu_1 - \mu_0)^2}}$$

where,

μ_0 = estimate for the mean of log (*survival*) for the control population

μ_1 = estimate for the mean of log (*survival*) for the treated population

$S_0{}^2$ = estimate for the variance of log (*survival*) for the control population

$S_1{}^2$ = estimate for the variance of log (*survival*) for the treated population

and variance = (number of events) x (standard error)^2.

Method: Testing the equation with real-world data

We tested this equation with the Scottish adjuvant tamoxifen trial (n=1323) which was initiated in 1978. In this trial, patients who had undergone surgery for breast cancer were randomly allocated to receive either tamoxifen for 5 years or not.

In 1978, it was not appreciated that tamoxifen only benefits patients with tumours that express the estrogen receptor (ER), so the trial included a significant number of patients with ER negative tumours. We now know that these ER negative patients would not have derived any benefit from tamoxifen.

Thus, this trial with mature data was ideal for testing whether our new equation could correctly estimate the proportion of patients who benefited from tamoxifen.

Conveniently, ER status was determined in the later years of the trial in 742 patients using the ligand-binding assay and expressed in fmol/mg protein.

Using the raw survival data from the trial we calculated the variances and survival times in each arm using the software SPSS version 13.0. Using these values in the new equation, we estimated the value of P and compared it with the actual proportion of patients who were ER positive.

Results - Does it work?

Our prediction:

Without using any information about the ER status, and only by using the length of survival of individual patients, our equation independently calculated that P = **64%** .

Thus, our equation **predicted** that **64% patients derived some benefit** from tamoxifen and **36% derived no benefit.**

The reality:

In 58.6% of patients the ER level was >19 fmol/mg and in 70.6% of patients it was >4 fmol/mg protein.

From the ER status, we now **know** that **59% to 71% patients benefited** from tamoxifen, and that **29% to 41% derived no benefit**.

Therefore, our prediction is consistent with reality.

This vindication of our insight using real clinical data also supports a biologically plausible view that there is a subpopulation amongst those treated that derive absolutely no benefit, while others may derive a variable amount of benefit.

Conclusion

Using raw survival data from a randomised trial, our method can estimate the proportion of patients that benefit from the new treatment.

We can thus foretell the existence and frequency of a previously unknown predictive factor (such as ER).

Our equation could be further verified using other datasets, such as the HERA trial in which some patients were not HER-2 positive and the ATAC trial in which some patients were not ER positive.

Impact

This Variance-Guided equation would be widely applicable to positive randomised clinical trials that have found an overall benefit from chemotherapy, hormone therapy, biologic therapy, or radiotherapy. From the raw data of these trials it will estimate whether everyone has benefited or only a proportion has benefit and if so, what is magnitude of that proportion.

In addition to the clinical benefit of a more precise consultation, such an estimate of the proportion of patients who actually benefit from a treatment could give us new biological and therapeutic insights into mechanisms of disease.

Estimation of the proportion of patients who benefit from a treatment in a positive randomised trial, using a novel Variance-Guided equation
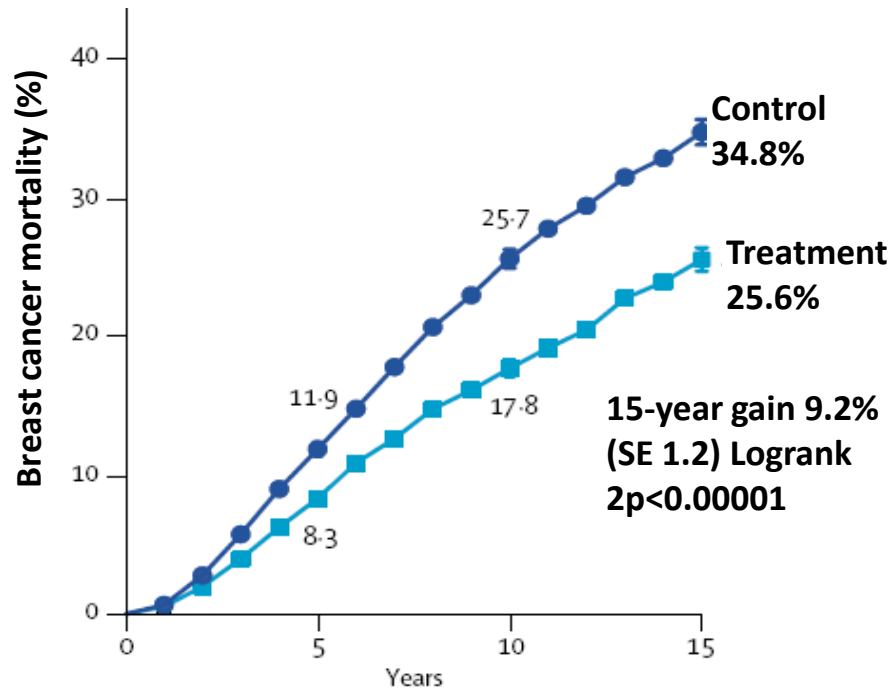
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The Problem

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Control 34.8%

Treatment 25.6%

15-year gain 9.2% (SE 1.2) Logrank 2p<0.00001

For example, from these data one can derive that there is a 9.2% reduction in mortality.

Does this mean...

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Or

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Or, most plausibly,

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Vaidya-Gadgil

A New Insight
# – A new Variance-Guided equation

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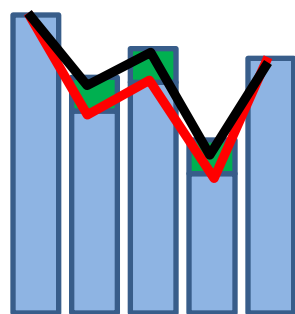
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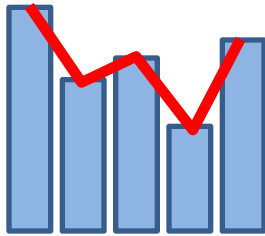
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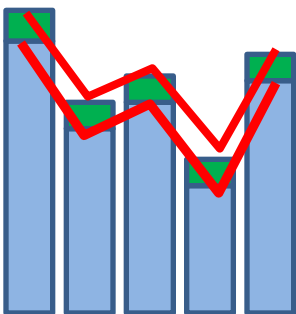
If only some benefit, the variance changes by an amount related to the proportion who benefit

$$P = \cfrac{1}{1 + \cfrac{S_1^2 - S_0^2}{(\mu_1 - \mu_0)^2}}$$

where,

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μ_1 = mean of log (*survival*) for the treated

S_0^2 = variance of log (*survival*) for the control

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variance = (number of events) x (standard error)^2

Vaidya-Gadgil

Testing the equation with real-world data

The Scottish adjuvant tamoxifen trial (n=1323)

Adjuvant tamoxifen vs. Not

1978 – NOT selected for ER status

Conveniently, ER status determined in 742

Using the raw survival data from the trial, we calculated the variances and survival times in each arm

Using these values in the new equation, we estimated the value of P and compared it with the actual % ER positive.

Results - Does it work?

Our prediction:

Without using any information about the ER status, our equation independently calculated that P = **64% derived some benefit.**

36% derived no benefit.

The reality:

In 58.6% ER > 19 fmol/mg protein

In 70.6%   ER > 4 fmol/mg protein

59% to 71% derived some benefit

29% to 41% derived no benefit.

Therefore, our prediction is consistent with reality

Could be further tested on other trials (HERA, ATAC, etc.)

Impact

- ❖ **Widely applicable to clinical trials of chemo-, hormone, radiation or biologic therapy**
- ❖ **Estimate the exact proportion who benefitted and who did not benefit**
    - ❖*A more precise consultation*
    - ❖*Get new biological and therapeutic insights into mechanisms of disease.*