# The Impact of Multi-Cancer Early Detection Tests on Cancer Mortality in the Context of Improving Cancer Survival

**#31931**

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## 1 BACKGROUND

- Cancer is the second leading cause of death in the United States.[1]
- Early detection could reduce cancer-related mortality by averting progression to late-stage cancer, which is associated with lower likelihood of cure and survival.[2,3]
- Currently, around half of cancer cases in the US are detected at an advanced stage,[4] and routine screening is USPTSF-recommended for only 4 cancer types (breast, cervical, colorectal, lung).[5]
- Blood-based multi-cancer early detection (MCED) tests could revolutionize cancer screening by simultaneously detecting multiple cancer types.
- **Cancer screening models typically use survival curves based on historical data. This neglects future improvements in cancer care and could lead to underestimation of the impact of the cancer screening tests.**

## 2 OBJECTIVE

To propose a method to model hypothetical improvements in cancer survival and its effect on mortality reduction yielded by supplemental screening with MCED test.

## 3 METHODS

### SiMCED

- We developed **Si**mulation Model for **MCED** (SiMCED), a microsimulation model of 14 solid tumor cancer types that account for ~80% of cancer incidence and mortality.[6]
- MCED test sensitivities were derived from a large, multi-center, prospectively-collected, retrospective case-control study (ASCEND 2).[7]
- After a cancer diagnosis, individuals follow survival curves to determine the time and cause of death, i.e., cancer- or non-cancer-related.
- We followed NICE Decision Support Unit (DSU) guidelines for survival curve fitting to select the optimal parametric model for each cancer type and stage.[8]
- Using a 10-year horizon, we simulated the life course of 5 million adults aged 50-84 years, representative of the US population.
- We compared outcomes under two screening strategies:
  - **Usual care:** No MCED testing, and;
  - **Usual care + MCED:** Annual MCED testing for individuals aged 50-84 years.
- **Scenario analysis:** In addition to *static survival*, we performed analysis using *dynamic survival*, i.e., hypothetical survival curves that emulate improving survival over time.

### Dynamic Survival

1. First, we estimated hazard ratios (HRs) of SEER 10-year survival at the cancer type-stage level between individuals diagnosed in 2010 versus an earlier reference year. We mapped the HRs from LRD to I-IV staging based on 2010-2021 incidence data. We present results using 1993 as the reference year (Figure 1).
2. We then applied HRs to the hazard function of the present-day survival curves in two different ways:
   - **Time-constant HRs:** HR is constant across all time points.
   - **Linearly decreasing HRs:** $HR(t)$ is a linearly decreasing function from $HR(0) = 1$ to $HR(17) = HR^*$, where $HR^*$ is the SEER-derived HR, i.e., $HR^*$ is attained in 2027. Beyond $t = 17$, $HR(t)$ was assumed to continue its linear decrease while enforcing non-negativity.
3. Finally, the adjusted survival curves were mathematically derived from the transformed hazard functions (Table 1).

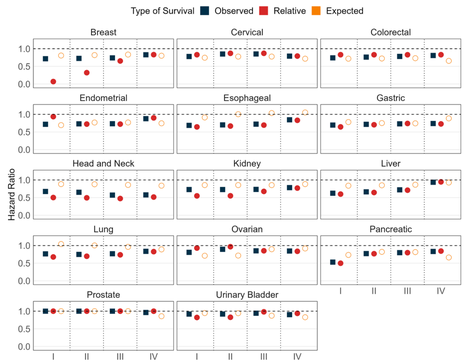


**Figure 1:** HRs of 10-year survival between individuals diagnosed in 2010 versus 1993.

**Table 1:** Unadjusted and adjusted hazard functions.

| Distribution | Hazard function | Adjusted hazard function |
|---|---|---|
| Gompertz | $\frac{b}{a}(e^{at}-1)$ | $\frac{b}{a}(e^{at}-1) - mb\frac{e^{at}(at-1)+1}{a^2}$ |
| Log-logistic | $\log\left(1+\left(\frac{t}{b}\right)^a\right)$ | $\log\left(1+\left(\frac{t}{b}\right)^a\right) - ma\int_0^t \frac{\left(\frac{u}{b}\right)^a}{1+\left(\frac{u}{b}\right)^a}\,du$ |
| Weibull | $\left(\frac{t}{\mu}\right)^a$ | $\left(\frac{t}{\mu}\right)^a - \frac{m\mu a}{a+1}\left(\frac{t}{\mu}\right)^{a+1}$ |
| Weibull PH | $\lambda t^a$ | $\lambda t^a - \frac{m\lambda a}{a+1}t^{a+1}$ |

The variable $m = (1 - HR^*)/17$ is the gradient of the linear decrease in $HR(t)$.

## 4 RESULTS

- Figure 2 shows adjusted and unadjusted survival curves for stage I breast cancer diagnosed at age 50-55 years, using the constant and linearly decreasing HR approaches.
- Table 2 displays overall cancer mortality outcomes (per 100,000) in each scenario.
- **Static survival:** Compared to **Usual Care**, supplemental screening with an MCED test reduced cancer mortality by 17% (2,611 versus 2,157).
- Among the cancer types for which there is no routine screening, the mortality reduction was 15% (1,196 versus 1,017).
- **Dynamic survival with time-constant HRs:** MCED screening resulted in a 20% (2,276 versus 1,815) 10-year mortality reduction.
- **Dynamic survival using linearly decreasing HRs:** MCED screening resulted in an 18% (2,564 versus 2,105) 10-year mortality reduction.
- Table 3 displays cancer-specific cancer mortality outcomes (per 100,000) in each scenario.

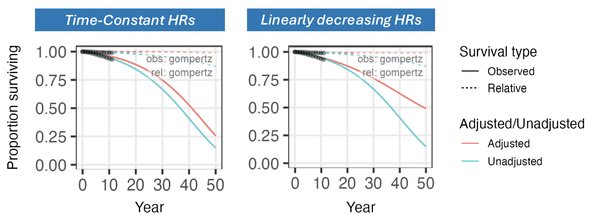


**Figure 2:** Unadjusted and adjusted survival curves for stage I breast cancer diagnosed at age 50-55 years using the constant and linearly decreasing HR approaches.

| Static survival | Usual care | Usual care + MCED | Absolute change | Relative change |
|---|---|---|---|---|
| Base case | 2,611 | 2,157 | -454 | -17% |
| **Dynamic survival** | **Usual care** | **Usual care + MCED** | **Absolute change** | **Relative change** |
| Time-constant HRs | 2,276 | 1,815 | -461 | -20% |
| Linearly decreasing HRs | 2,564 | 2,105 | -460 | -18% |

**Table 2:** Overall cancer mortality outcomes (per 100,000) by scenario.

**Table 3:** Cancer-specific cancer mortality outcomes (per 100,000) by scenario.

| | Static survival | | | | Dynamic survival with time-constant HRs | | | | Dynamic survival with linearly decreasing HRs | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cancer** | **Usual care** | **Usual care + MCED** | **Absolute change** | **Relative change** | **Usual care** | **Usual care + MCED** | **Absolute change** | **Relative change** | **Usual care** | **Usual care + MCED** | **Absolute change** | **Relative change** |
| Breast | 127 | 91 | -35 | -28% | 93 | 61 | -31 | -34% | 120 | 85 | -35 | -29% |
| Cervical | 22 | 12 | -10 | -44% | 20 | 11 | -9 | -46% | 22 | 12 | -10 | -45% |
| Colorectal | 293 | 194 | -99 | -34% | 259 | 168 | -91 | -35% | 288 | 190 | -98 | -34% |
| Endometrial | 60 | 47 | -13 | -22% | 53 | 40 | -13 | -24% | 58 | 46 | -13 | -22% |
| Esophageal | 84 | 74 | -10 | -12% | 72 | 61 | -12 | -16% | 83 | 72 | -10 | -12% |
| Gastric | 108 | 83 | -25 | -24% | 91 | 67 | -25 | -27% | 106 | 80 | -26 | -24% |
| Head and Neck | 115 | 96 | -19 | -16% | 67 | 55 | -12 | -18% | 108 | 89 | -19 | -17% |
| Kidney | 94 | 81 | -12 | -13% | 74 | 63 | -11 | -15% | 91 | 79 | -12 | -13% |
| Liver | 181 | 146 | -36 | -20% | 155 | 113 | -41 | -27% | 178 | 141 | -37 | -21% |
| Lung | 973 | 843 | -129 | -13% | 876 | 733 | -144 | -16% | 960 | 827 | -133 | -14% |
| Ovarian | 72 | 63 | -9 | -12% | 66 | 58 | -8 | -12% | 71 | 62 | -9 | -12% |
| Pancreatic | 302 | 258 | -44 | -14% | 277 | 225 | -51 | -19% | 300 | 254 | -45 | -15% |
| Prostate | 88 | 86 | -2 | -2% | 88 | 86 | -2 | -2% | 88 | 86 | -2 | -2% |
| Urinary Bladder | 93 | 81 | -12 | -13% | 85 | 74 | -11 | -13% | 92 | 80 | -12 | -13% |
| **Total** | 2,611 | 2,157 | -454 | -17% | 2,276 | 1,815 | -461 | -20% | 2,564 | 2,105 | -460 | -18% |

## 5 CONCLUSIONS

- Supplemental MCED screening could be effective for reducing both stage IV cancer incidence and mortality across multiple cancer types.
- Adjusting survival to account for future improvements in cancer care increases the estimated potential benefits of MCED tests, and suggests that traditional modeling may underestimate its true impact.
- Implementing dynamic survival to reflect continual improvement in cancer survival, could enhance the value of interventions for early detection of cancer.

**Implementation of dynamic survival in cancer screening models can improve the accuracy of cancer mortality forecasting and enhance the value of early cancer detection.**

## 6 REFERENCES

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This study was funded by Exact Sciences Corp., Madison, WI.