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# Figures and figure supplements

Dynamics of preventive vs post-diagnostic cancer control using low-impact measures

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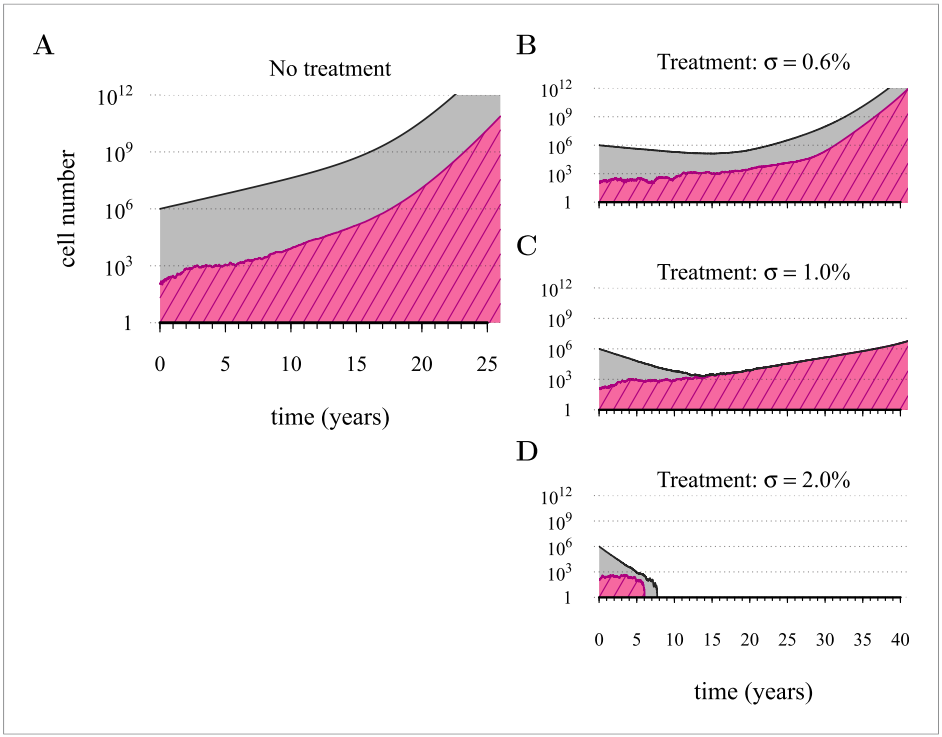


**Figure 1**. Treatments curb or eliminate tumours. Examples of single patient tumour growth for (**A**) no treatment. (**B**) $\sigma$ = 0.6%. (**C**) $\sigma$ = 1.0%. (**D**) $\sigma$ = 2.0%. The shaded area shows the change in total tumour size and the hatched area, the resistant part of a tumour. The treatment intensity σ in this and all other figures are represented as cell arrest per day (σ/4). Parameter values as in ***Table 1***.

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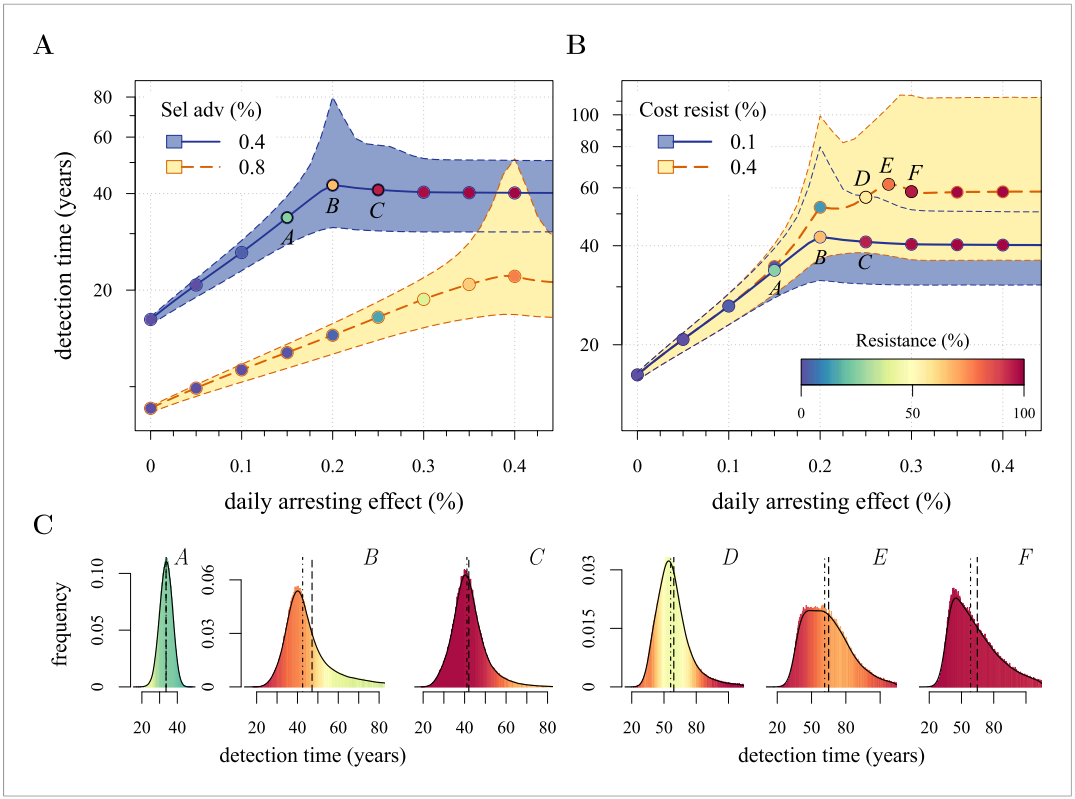


**Figure 2**. Treatment level affects both detection time and frequency of resistance. The median (lines) and 90% confidence intervals (shaded areas) of detection times, measured as years beyond the initiation of the preventive measure. Effects of: (**A**) the selective advantage of each additional driver and (**B**) the cost of resistance. (**C**) Samples of the distribution of detection times (in relative frequencies, adjusted for 3-month bins) for corresponding points, indicated in **A** and **B**. Dashed black line is the mean and the dashed-and-dotted line is the median. The colour-code indicates the average level of resistance in detected tumours over 3 month intervals (see inset in **B**). All cells $j = 0$ at $t = 0$. Other parameters as in ***Table 1***. Detection time is log-transformed in **A** and **B**.

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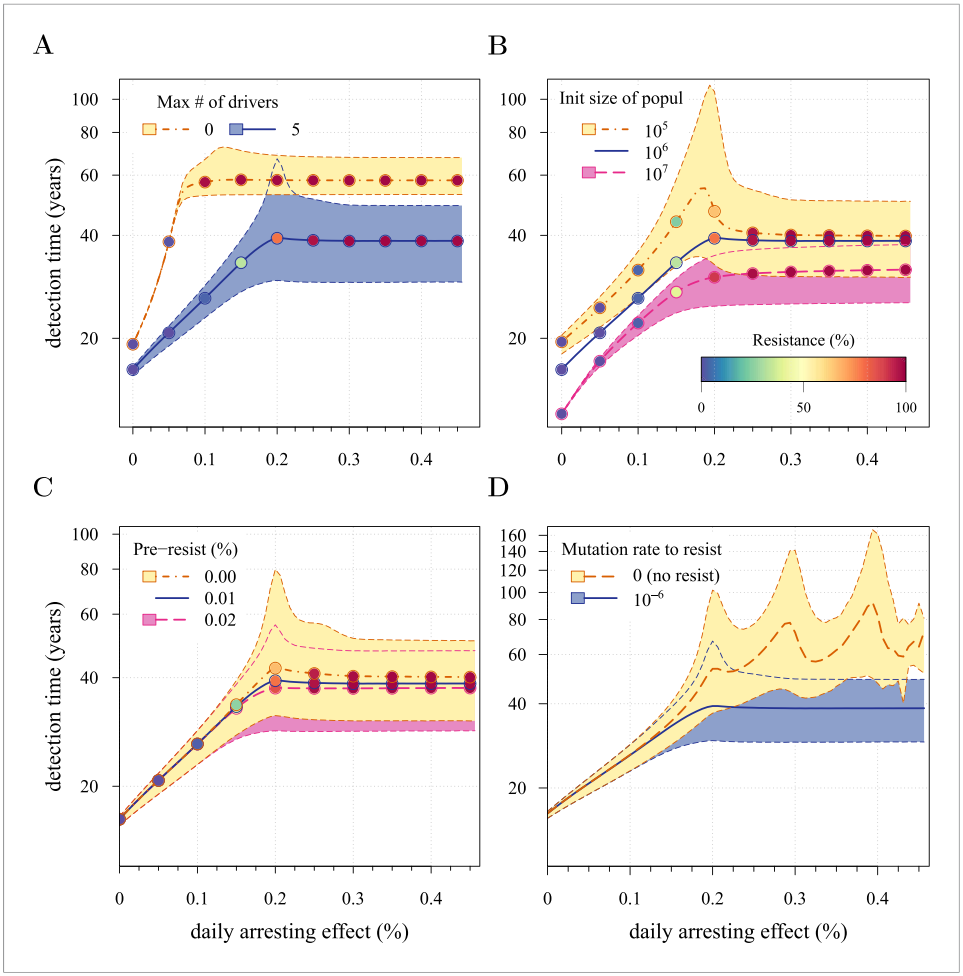


**Figure 2—figure supplement 1**. Sensitivity analysis for several key parameters. (**A**) Maximal number of additionally accumulated drivers. (**B**) Initial cell number. (**C**) Level of initial partial resistance of a tumour. (**D**) Presence or absence of resistant cell-lines. Point colour-codes indicate the average level of resistance in detected tumours over 3 month intervals (see inset in **B**). For simplicity, only the median is indicated in **B** and **C** for the baseline case (blue line). Lines and shading otherwise as in ***Figure 2***. Unless otherwise stated, parameter values as in ***Table 1***.

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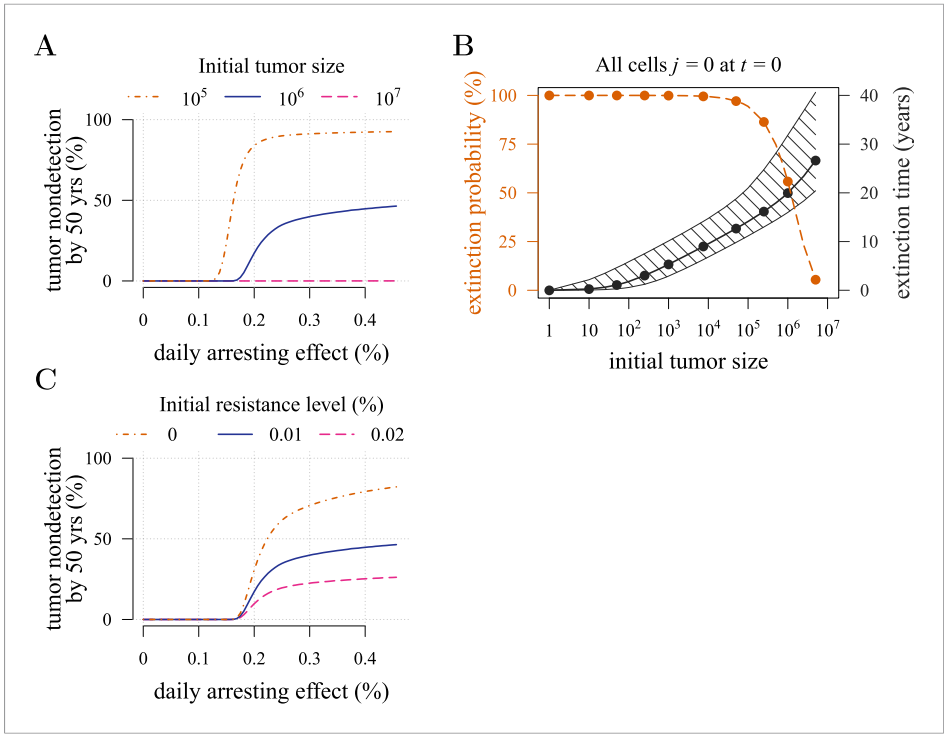


**Figure 2—figure supplement 2**. Effects of initial neoplasm size (**A**, **B**) and resistance level (**C**) on preventive measure success. Success is defined as tumour non-detection by 50 years. Daily effect of treatment on cellular arrest is assumed to be 0.25%. Unless otherwise stated, parameter values as in ***Table 1***.

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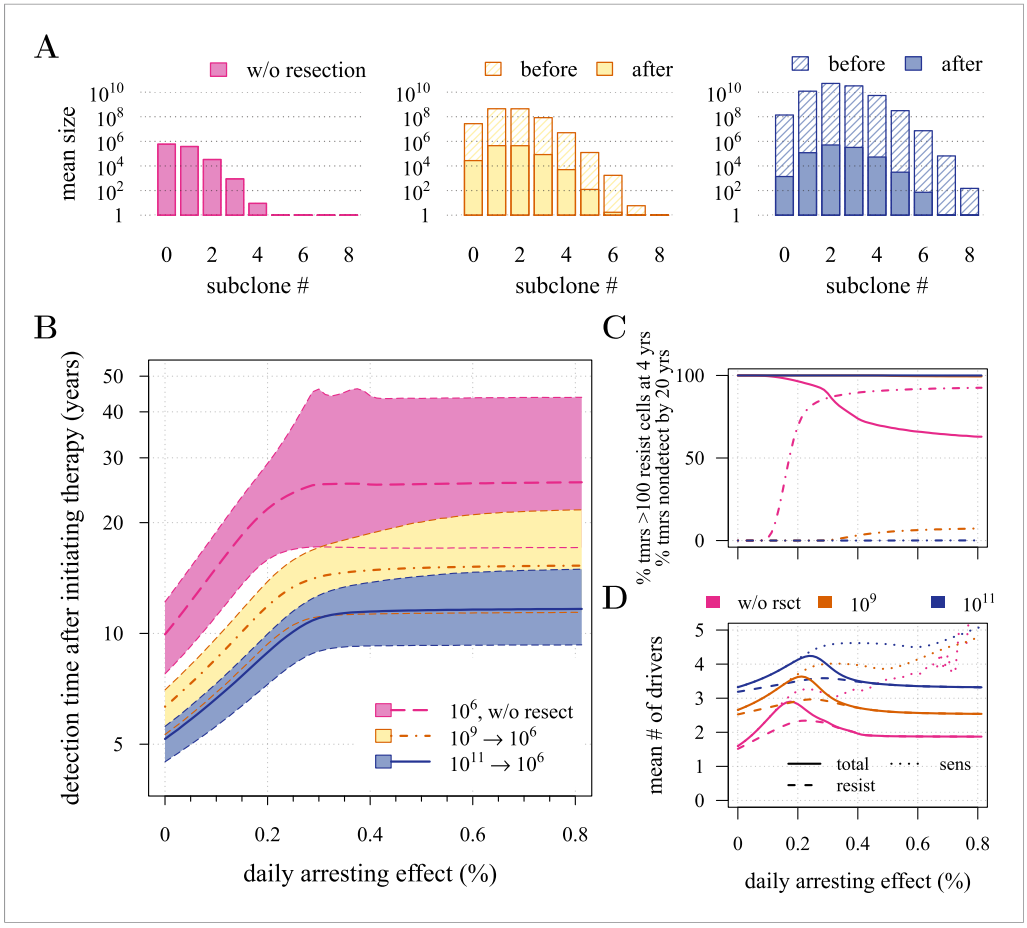


**Figure 3**. Effects of preventive and post-diagnostic interventions against tumours consisting of 1 million cells. (**A**) The distribution of mean sizes of subclones (hatched bars = before removal and solid bars = post removal). (**B**) The time distribution of cases in which either intervention type fails to control the tumour below the detection threshold after 50 years (thick line = median, filled area with dashed boundaries = 90% CIs) for different constant treatment intensities. (**C**) The percentage of cases where the tumour consists of less than 100 resistant cells at 4 years after treatment commences (solid lines), and the percentage of cases where tumour size is below the detection threshold 20 years after the measure begins (dashed-and-dotted lines). (**D**) The mean number of accumulated drivers within a tumour at the time of detection. Parameter values as in ***Table 1***.

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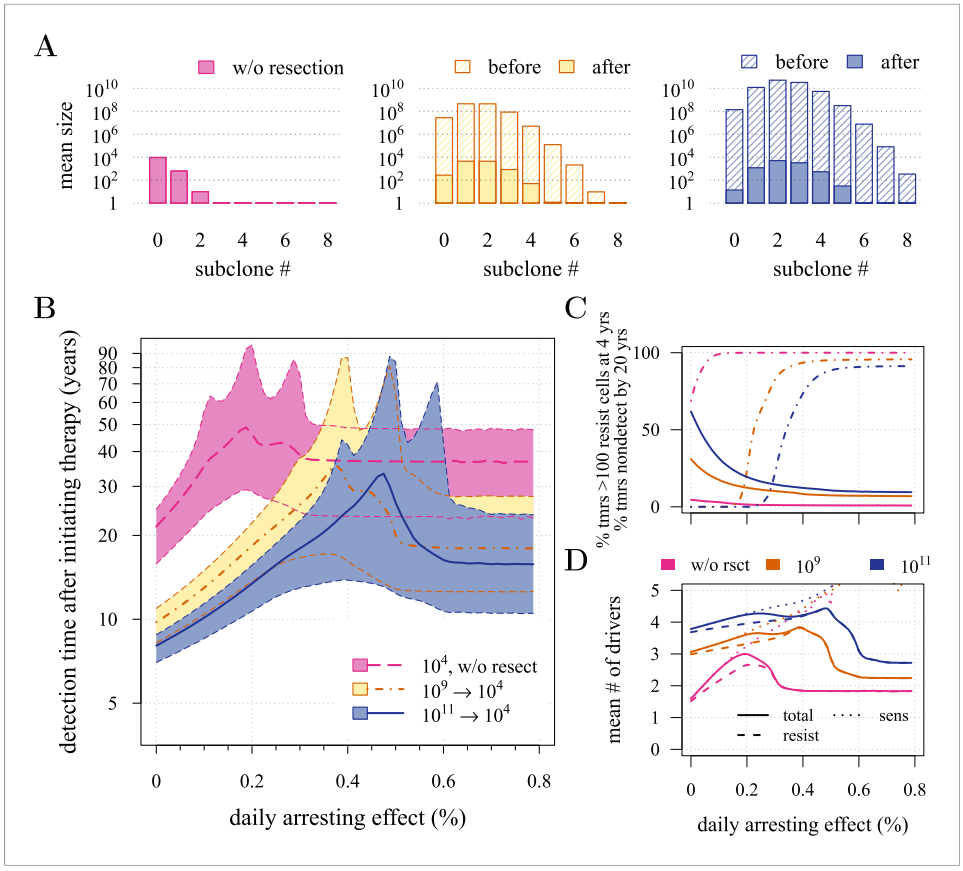


**Figure 3—figure supplement 1**. Effects of preventive and post-diagnostic interventions against tumours consisting of 10,000 cells. Same as ***Figure 3***, except interventions against $10^4$ cancer cells. (**A**) The distribution of mean sizes of subclones for different constant treatment intensities (hatched bars = before removal and solid bars = post removal). (**B**) The time distribution of cases in which either intervention type fails to control the tumour below the detection threshold after 50 years (thick lines = medians, shaded areas with dashed boundaries = 90% CIs). (**C**) The percentage of cases when a tumour consists of less than 100 resistant cells at 4 years post-resection (solid lines) and the percentage of cases when tumour sizes are below the detection threshold 20 years after the measure commences (dashed-and-dotted lines). (**D**) The mean number of accumulated drivers within a tumour at the time of detection. Parameter values as in ***Table 1***.

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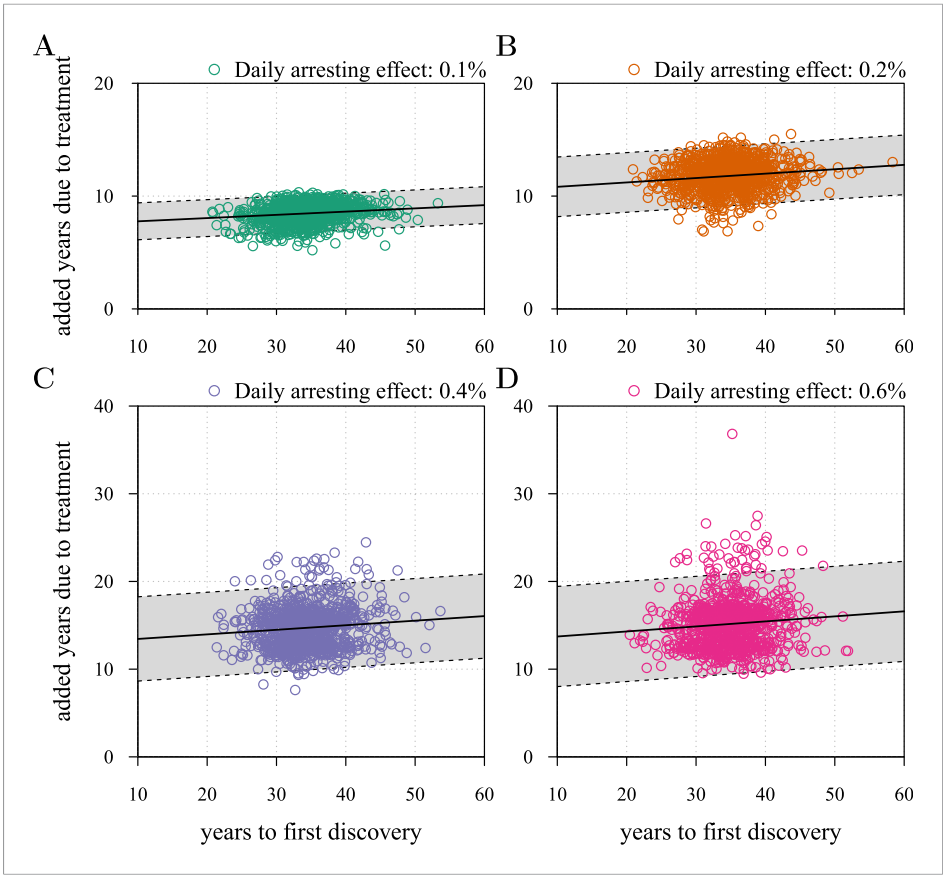


**Figure 3—figure supplement 2**. Time to first discovery as a predictor of post-diagnostic treatment success. Time to tumour relapse following resection as function of the time it takes for the initial cancer cell to attain $10^9$ cells (i.e., the point at which the tumour is discovered, resected, and treatment begins). Each dot represents a numerical simulation from the yellow distribution in ***Figure 3B*** (only 1,000 simulation results out of $10^6$are shown). Four different treatment levels are considered. Black solid line is a simple linear regression, and grey area with dashed boundaries indicates extrapolation of high and low bounds accounting for 95% of observations (prediction interval). The fitted linear regression model gives an intercept of 7.5 years, a slope of 1.6˚ and $R^2$ of 0.024 in (**A**), 10.4 years, 2.2˚ and $R^2$ of 0.017 in (**B**), 12.9 years, 3.0˚ and $R^2$ of 0.009 in (**C**), and 13.1 years, 3.3˚ and $R^2$ of 0.008 in (**D**). Parameters as in ***Table 1***.
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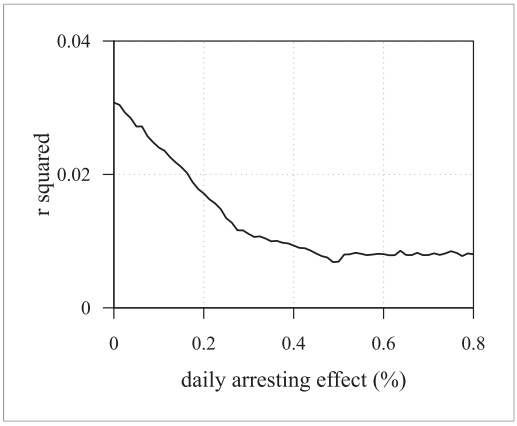


**Figure 3—figure supplement 3**. The R2 of regressions from numerical experiments for different treatment levels of time to tumour relapse following resection as function of the mean number of drivers in a resected tumour. Time to tumour discovery is generally more predictive of post-diagnostic therapeutic outcome for lower treatment levels. See ***Figure 3—figure supplement 2*** for details.
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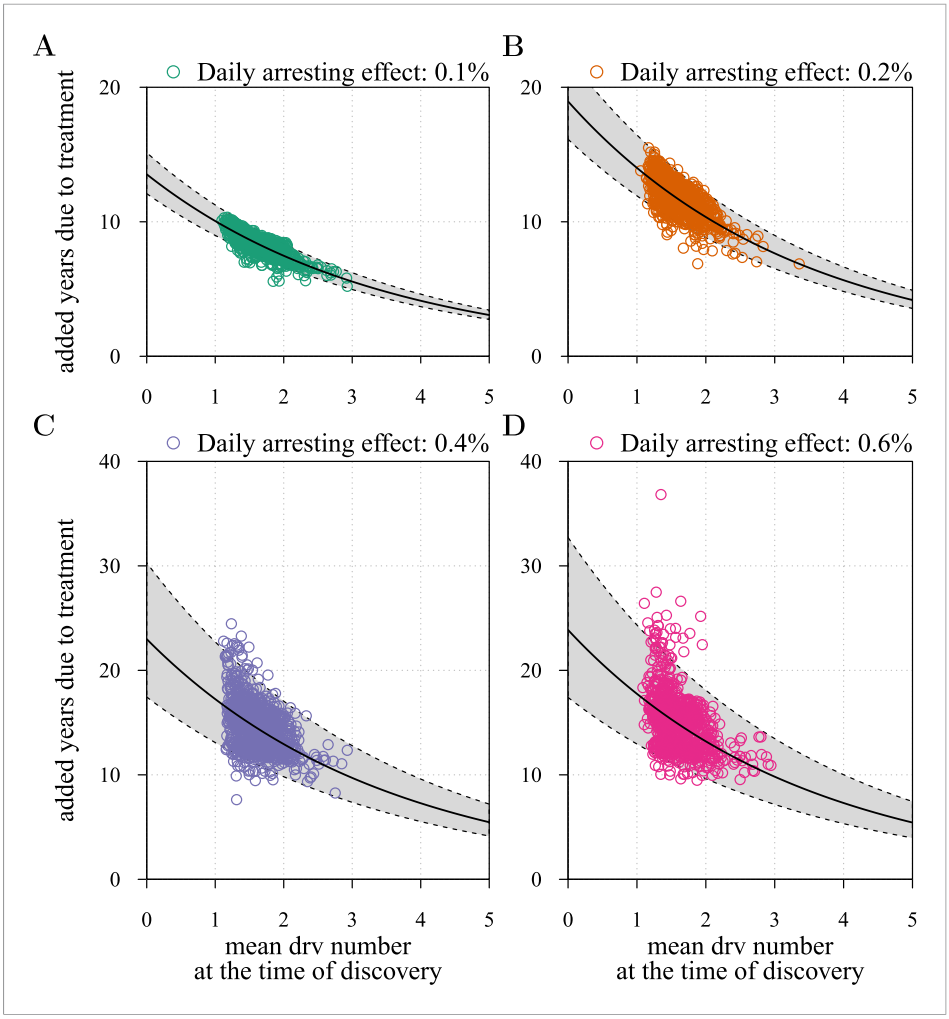


**Figure 3—figure supplement 4**. Mean number of additionally accumulated drivers in resected tumour as a predictor of post-diagnostic treatment success. The fitted negative exponential regression model $y = ae^{-bx}$ gives $a = 13.5$ years, $b = 0.3$ and $R^2 = 0.696$ in (**A**), 18.95 years, 0.3 and $R^2 = 0.537$ in (**B**), 23.0 years, 0.29 and $R^2 = 0.262$ in (**C**), and 23.9 years, 0.3 and $R^2 = 0.224$ in (**D**). See ***Figure 3—figure supplement 2*** for details.
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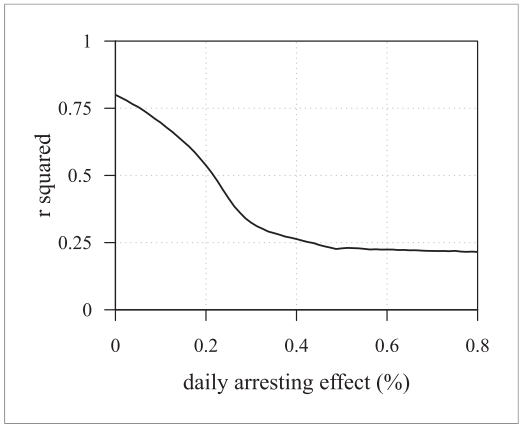


**Figure 3—figure supplement 5**. The $R^2$ of regressions from numerical experiments for different treatment levels of time to tumour relapse following resection as function of the mean number of drivers in a resected tumour. Time to tumour discovery is more predictive of post-diagnostic therapeutic outcome for lower treatment levels. See ***Figure 3—figure supplement 4*** for details.

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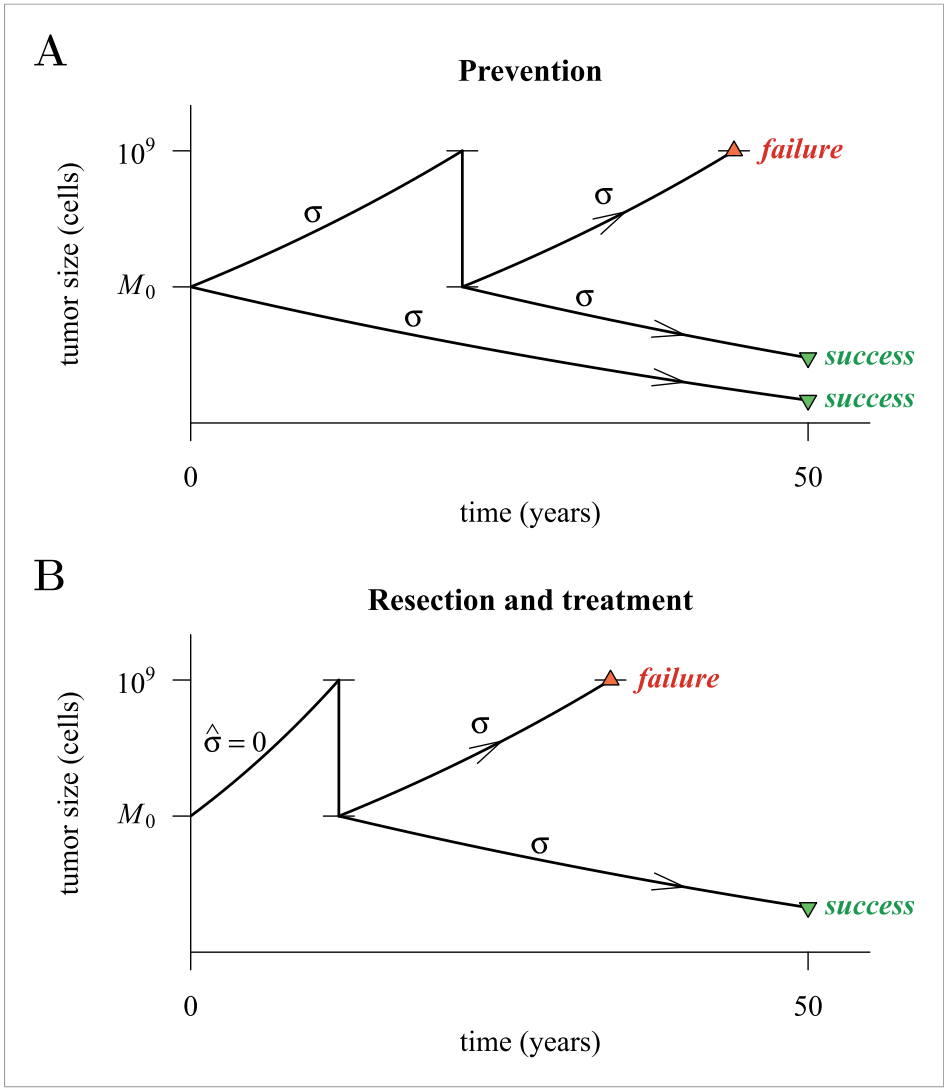


**Figure 4**. Hypothetical process of preventive (with a 'second chance') and post-diagnostic measures. A tumour is initiated by one cell and grows to size $M_0$ (either $10^4$ or $10^6$ cells in our numerical studies). Prevention (**A**) arrests tumour growth at intensity $\sigma$ (daily level = $\sigma/4$). Should the tumour grow to $10^9$ cells, it is diagnosed and resected to $M = M_0$ cells and then treated again at intensity $\sigma$. Post-diagnostic intervention (**B**) does not discover the growing tumour until $10^9$ cells (i.e., $\sigma = \hat{\sigma} = 0$), whereupon it is resected to $M = M_0$ cells and then treated at intensity $\sigma > 0$. Either intervention finally 'fails' should the tumour attain $10^9$ cells a second time, no later than 50 years after the initial lesion of size $M_0$. Should the tumour be eradicated or not exceed $10^9$ cells by 50 years after the initial lesion, then the intervention is deemed a 'success'.

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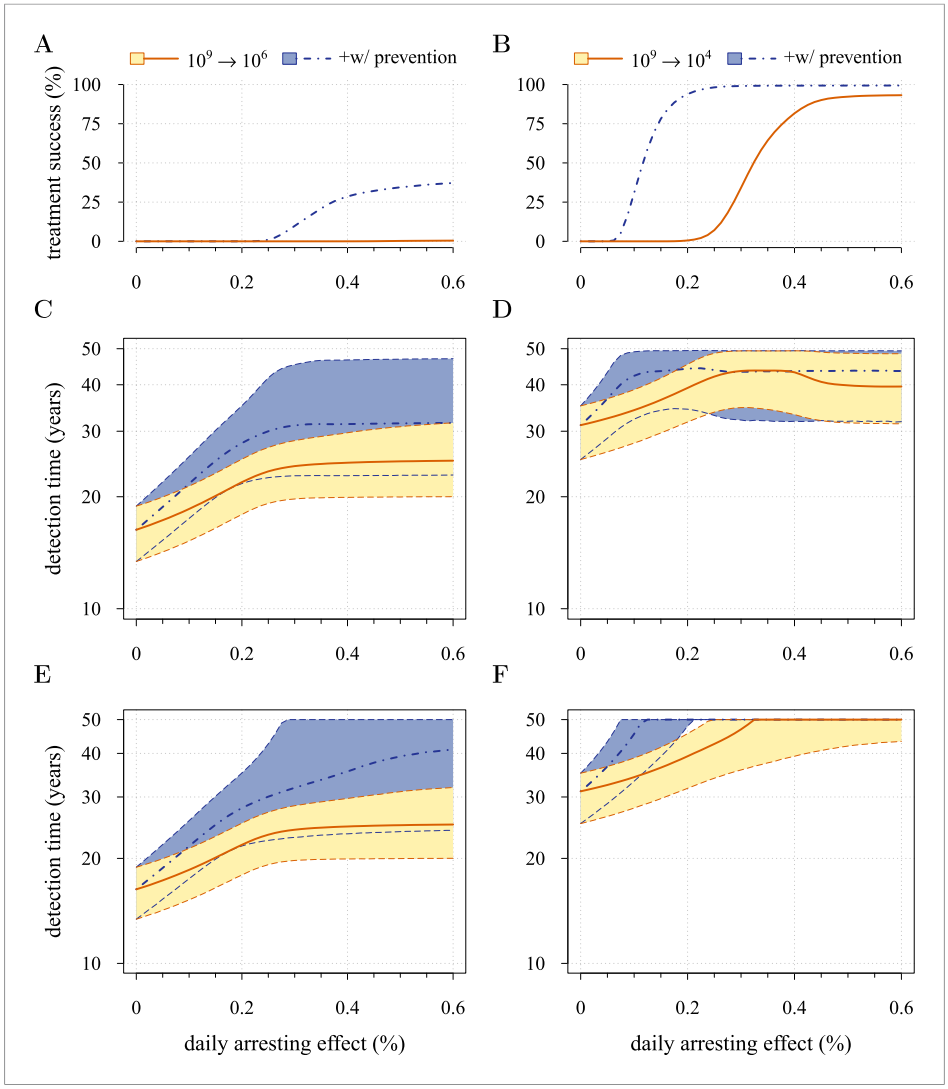


**Figure 5**. Comparison of preventive (blue lines and shading) and post-diagnostic (red lines, yellow shading) interventions. Tumours are either treated at $M_0 = 10^6$ cells (left panels) or $M_0 = 10^4$ cells (right panels). (**A**, **B**) Probability of treatment success, defined as the proportion of cases where the tumour remains undetected (either extinct or below $10^9$ cells) by 50 years after the initial lesion of $M_0$ cells. (**C**, **D**) Distribution of times to relapse for treatment failures. (**E**, **F**) Distribution of detection times for all cases including relapsed tumours and tumours remaining undetected prior to and after 50 years (detection times are assigned to 50 years in the latter case). Parameters as in ***Table 1***. See ***Figure 3*** for details.

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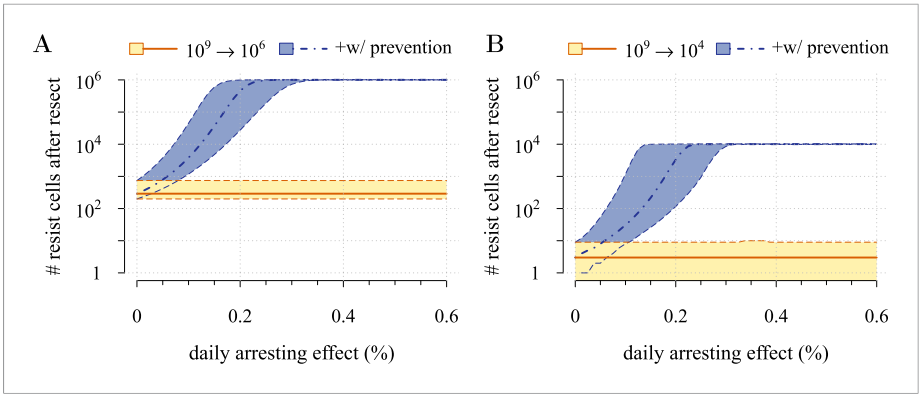


**Figure 5—figure supplement 1**. Resistant cell populations after initial failure. Tumours are either treated at $M_0$ = $10^6$cells (**A**) or $M_0$ = $10^4$cells (**B**). Red lines and yellow shading = population following resection. Parameter values as in ***Table 1***.

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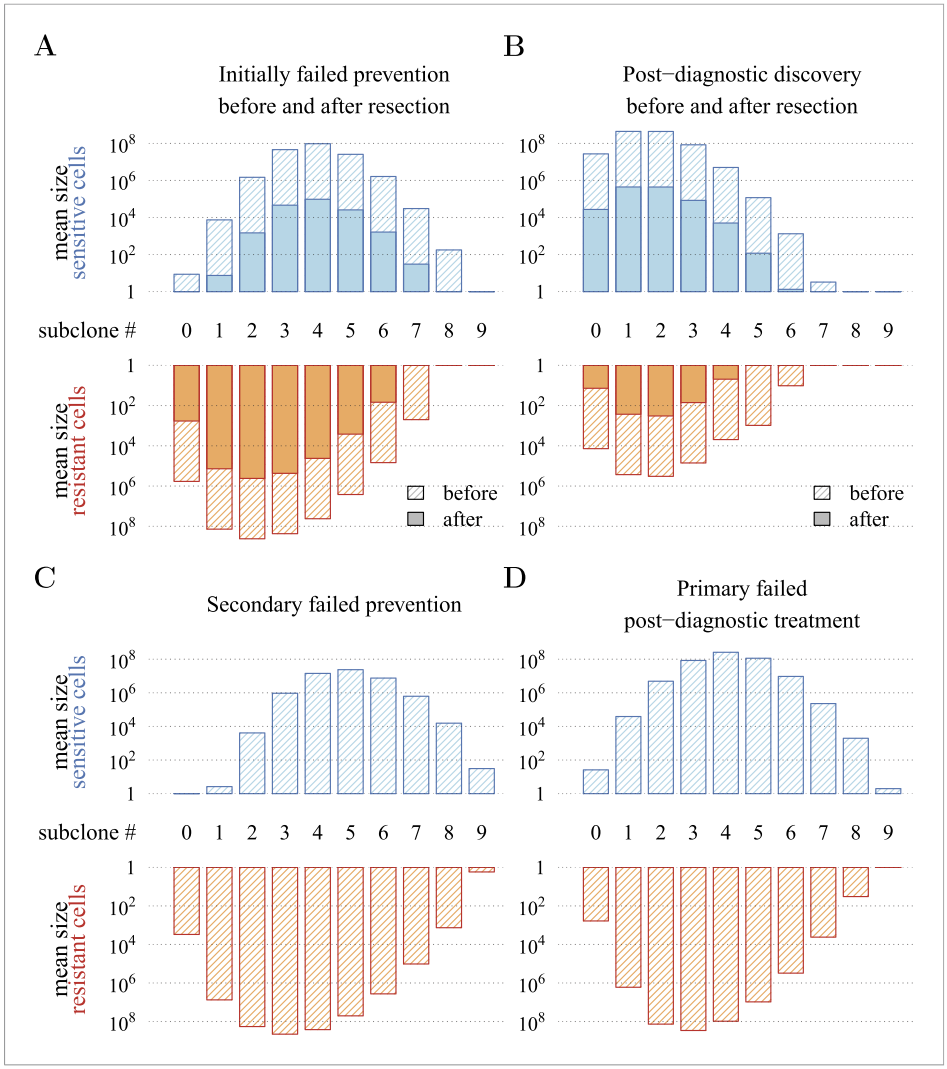


**Figure 5—figure supplement 2**. Distribution of mean sizes of subclones. (**A**) Cases where a tumour is detected and resected following prevention. (**B**) Cases where a tumour is detected and resected with no prevention. (**C**) Cases of relapse following resection and secondary treatment to initially failed prevention. (**D**) Cases of relapse following resection and primary treatment in cases where there was no prevention. Hatched bars indicate cell numbers in the tumour and solid bar numbers after resection and $10^6$ residual or metastatic cells. Daily arresting level assumed to be 0.25%. Parameter values as in ***Table 1***.

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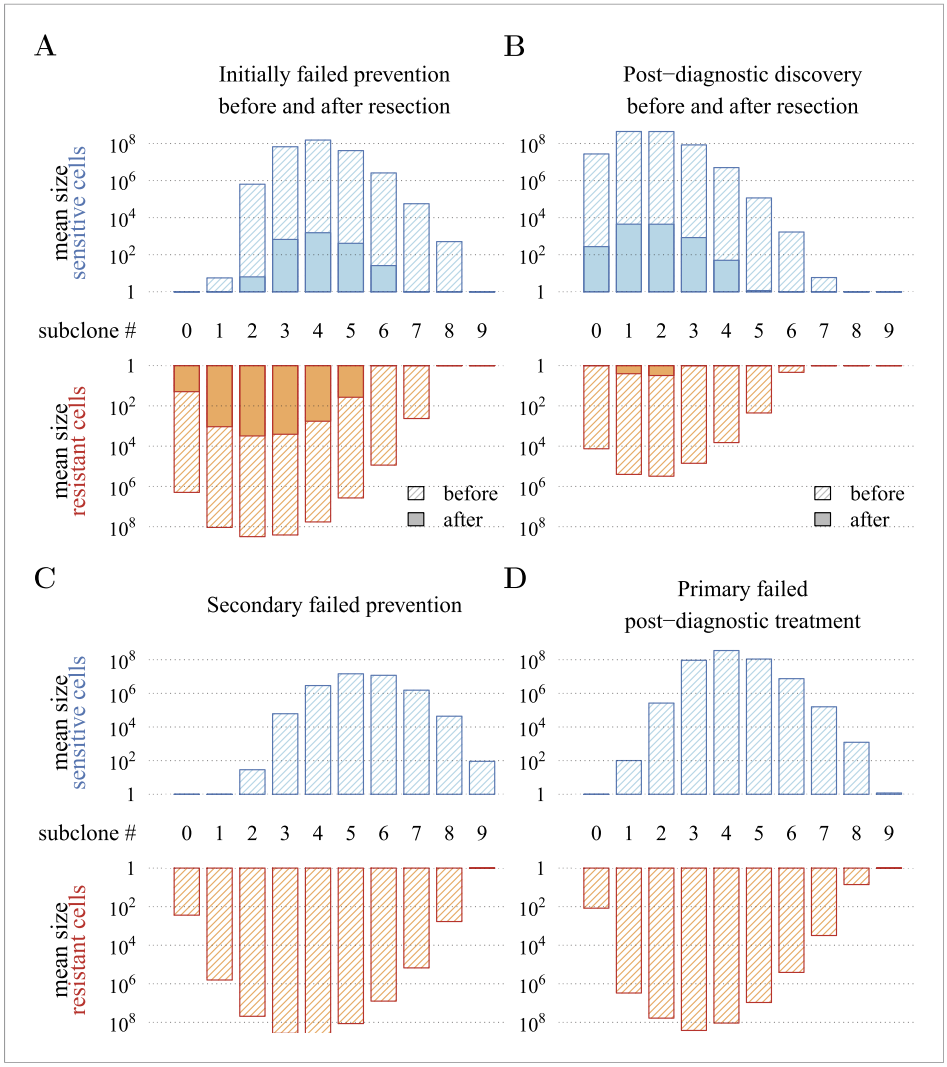


**Figure 5—figure supplement 3**. Distribution of mean sizes of subclones. Same as ***Figure 5—figure supplement 2***, except $M_0$ is $10^4$ cancer cells.

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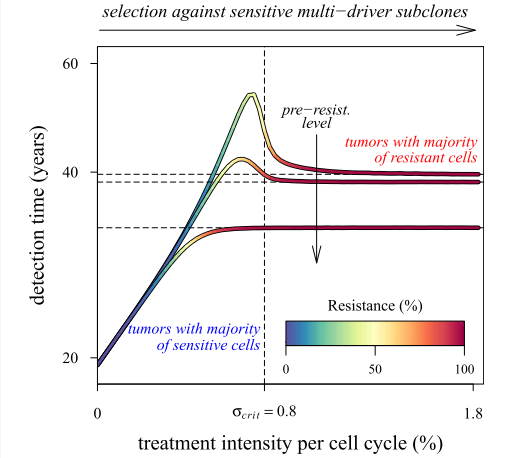


**Figure 6**. Dependence of the median time for tumour detection on treatment intensity and pre-resistance levels. Increasing treatment intensity selects against subclones with increasing numbers of drivers, whereas, regardless of treatment intensity, all resistant subclones with $s(i+1) > c$ increase in number. The solid lines illustrate how selection and the initial number of resistant cells in a treated tumour predict median detection times and associated resistance levels. Median detection times approach a horizontal asymptote at 100% resistance as treatment intensity increases, whereas if the resistant mutation were to be knocked out, then the vertical asymptote at $\sigma_{crit} = qs$ (where $q$ is the number of drivers in the fastest growing subclone) would be approached instead for sufficiently small tumours. Asymptotes are shown as dashed lines. We illustrate three cases, each with an initial population of 100,000 identical cells ($i = 0$) and with one of three different initial numbers of resistant cells: 10, 100 or 1,000 (top to bottom lines). Other parameters as in ***Table 1***.

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