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Appendix

Impact of disruptions and recovery for established cervical screening programs across a range of high-income country program designs, using COVID-19 as an example: a modelled analysis

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Additional information on methods

Upstaging cancers

It was not possible in the models to track changes in cancer diagnoses or stage shifting in individual women. Consequently, in order to calculate the number of cancers which were upstaged, we needed to make some assumptions, which were as follows:

i) Cancers would only be upstaged to the next most serious stage (eg cancers would not be upstaged from localized to distant within a year) – on the basis that the disruption periods where relatively short (no more than 12 months) and recovery was rapid
ii) Based on i), any additional cancers detected in the most serious stage were assumed to have been upstaged from the next most serious (eg from regional to distant)
iii) Additional cancers (resulting from a missed visit in 2020, and which would otherwise have been detected at the precancer stage in the absence of disruptions) were assumed to be localized
iv) Differences in the number of cancers detected in specific stages in the disruption compared to the no disruption scenario not already explained by ii) and iii) were assumed to have been upstaged eg from localized to regional.

Calculations for an example scenario are shown below.

Table A1 - Sample table for calculating upstaging

	Local [L]	Regional [R]	Distant [D]
Scenario X (with disruption)	x	y	z
Scenario 0 (no disruption counterfactual)	a	b	c

Upstaged [R to D] = z - c

y = b + Upstaged [L to R] - Upstaged[R to D]

=> Upstaged [L to R] = y - b + Upstaged [R to D]

= y - b + z - c

Total upstaged = Upstaged [L to R] + Upstaged [R to D]

Additional deaths resulting from additional and upstaged cancers

In order to capture the longer term impact of both additional and upstaged cancers on cervical cancer deaths, calculations for additional deaths were not restricted to the period 2020-2030.

All models produced results for cancer diagnoses by stage (localized/ regional/ distant for Australia, Norway and USA models; FIGO stages for Netherlands model), but varied in the structure and detail of survival assumptions for women diagnosed with cervical cancer. In the Australia, Netherlands and USA-Policy1 models, women diagnosed with cervical cancer were assumed to have an increased risk of death for the first 10 years after diagnosis (which varied by stage), but after 10 years, relative survival compared to same-age women was assumed to be 1. Additional cancer deaths in these models were calculated by applying stage-specific survival assumptions to the total number of cancer cases diagnosed over 2020-2030 for each scenario, and calculating the difference compared to the no disruption scenario (S0). Survival assumptions in these models are included in Table A2, Table A3, and Table A4. As survival varied by mode of cancer detection (screening vs symptoms), a range was calculated by assuming either all additional/ upstaged cancers were screen-detected (lower end) or all additional/ upstaged cancers were symptomatically-detected (upper end). The Harvard models for Norway and the USA assumed excess mortality for women diagnosed with cervical cancer for up to 20 years. Excess deaths in the two Harvard models were calculated by running each scenario out to 2050, to ensure that the full period of excess mortality was taken into account, and the difference in deaths between each disruption scenario run and the no disruption scenario (S0) was calculated directly from model-predicted deaths over 2020-2050.

Table A2 – Cervical cancer survival assumptions used to calculate additional cancer deaths: Netherlands (MISCAN) model

Stage at diagnosis	Probability of survival (cure) after 10 years
FIGO1A	0.9643
FIGO1B	0.8553
FIGO2	0.6623
FIGO3	0.3243
FIGO4	0.091

Table A3 - Cervical cancer survival assumptions used to calculate additional cancer deaths: Australia model

Stage at diagnosis	Probability of survival (cure) after 10 years	
	Screen-detected	Symptomatically-detected
Localized	0.9161	0.794
Regional	0.6235	0.5331
Distant	0.2221	0.1899

Table A4 - Cervical cancer survival assumptions used to calculate additional cancer deaths: USA (Policy1) model

Stage at diagnosis	Probability of survival (cure) after 10 years	
	Screen-detected	Symptomatically-detected
Localized	0.908	0.794
Regional	0.6708	0.5331
Distant	0.3544	0.1899

Supplementary results

The predicted impact of the 6-month disruption scenarios (ie 6-month equivalent of the results in **Error! Reference source not found.** in the main text) are provided in Table A5.

Absolute case numbers (women who miss screening, additional and upstaged cancers, additional deaths resulting from additional and upstaged cancers) for settings with a single screening modality nationally (Australia and the Netherlands) are provided in Table A6.

Table A5 - Predicted impact of disruptions on women screened, and cancer diagnoses over 2020-2030 and related deaths, by setting: 6-month scenarios

Setting	Disruptions include	Women predicted to miss screening visits[1]	Cervical cancer cases (2020-2030) [1]				Predicted additional deaths due to additional/ upstaged cancers in 2020-2030[1]
			Expected (no disruptions)	Additional due to disruptions	% increase	Detected at higher stage	
Australia	Primary Scr (S1):	53,565.0		4.3	0.5	1.6	0.9 - 1.4
	Surveillance (S2):	58,009.6	791.5	7.6	1.0	3.6	1.8 - 2.6
	Colp/Tx (S3):	58,009.9		11.6	1.5	5.6	2.9 - 4.0
Netherlands	Primary Scr (S1):	33,670.2	1,144.1	1.2	0.1	0.4	0.2
Norway (cytology)*	Primary Scr (S1):	89,023.3		0.1	0.0	0.9	1.3
	Surveillance (S2):	89,023.3	1,510.1	3.6	0.2	2.2	4.3
	Colp/Tx (S3):	89,023.3		5.3	0.4	2.3	5.2
Norway (primary HPV)*	Primary Scr (S1):	65,096.0		1.6	0.1	0.8	0.8
	Surveillance (S2):	65,096.0	1,321.6	6.1	0.5	2.4	5.3
	Colp/Tx (S3):	65,096.0		8.1	0.6	2.6	6.3
USA (cytology) *Harvard**	Primary Scr (S1):	107,543.1		0.4	-	0.9	-
	Surveillance (S2):	107,543.1	788.7	1.3	0.2	1.1	-
	Colp/Tx (S3):	107,543.1		3.5	0.4	1.6	0.1
USA (co-testing) *Harvard**	Primary Scr (S1):	107,100.3		-	-	-	-
	Surveillance (S2):	107,100.3	236.3	0.8	0.3	-	-
	Colp/Tx (S3):	107,100.3		2.4	1.0	-	-

USA (cytology) *Policy1**	Primary Scr (S1):	99,085.8		1.3	0.2	0.1	0.1 - 0.3
	Surveillance (S2):	107,315.0	606.8	2.5	0.4	0.1	0.3 - 0.6
	Colp/Tx (S3):	107,315.0		5.2	0.9	0.6	0.7 - 1.3
USA (co-testing) *Policy1**	Primary Scr (S1):	92,462.2		1.1	0.3	1.3	0.4 - 0.6
	Surveillance (S2):	113,755.7	384.9	5.1	1.3	1.1	0.8 - 1.3
	Colp/Tx (S3):	113,755.7		5.6	1.5	0.7	0.7 - 1.4

na = not available 1. Values are per million women aged 20+ in 2020. Lower disease level in Harvard US model in the no disruption scenario is partially due to the model reflecting squamous cell carcinoma only. Number of deaths is presented as a range in cases where the model assumes survival varies by mode of detection (screening vs via symptoms); the lower end assumes additional/ upstaged cancers are detected via screening and the upper end assumes additional/ upstaged cancers are detected via symptoms.

Table A6 – Absolute case numbers for settings with a single screening modality nationally (Australia and the Netherlands)

Setting	**Disruptions include**	**Women predicted to miss screening visits**	**Cervical cancer cases (2020-2030) [1]**				**Predicted additional deaths due to additional/ upstaged cancers in 2020-2030 [1]**
			Expected (no disruptions)	**Additional due to disruptions**	**% increase**	**Detected at higher stage**	
Australia	Primary Scr (S1,S5):	513,720 – 1,027,440		41 - 82	0.55% - 1.1%	15 - 30	8 - 17
	Surveillance (S2, S6):	556,346 – 1,112,692	7,510	72 - 137	0.96% - 1.82%	34 - 65	17 - 33
	Colp/Tx (S3,S7):	556,349 – 1,112,698		110 - 196	1.47% - 2.61%	54 - 96	27 - 48
Netherlands	Primary Scr (S5):	228,666 – 457,333	7,770	8 - 27	0.1% - 0.35%	2 - 10	3 - 4

Values are rounded to the nearest whole number. Range represents the range across 6- and 12-month scenarios. na = not available. Number of deaths is presented as a range in cases where the model assumes survival varies by mode of detection (screening vs via symptoms); the lower end assumes additional/ upstaged cancers are detected via screening and the upper end assumes additional/ upstaged cancers are detected via symptoms.

Supplementary charts

Figure A1 – predicted cervical cancer cases over 2020-2030 per million women aged 20+ years

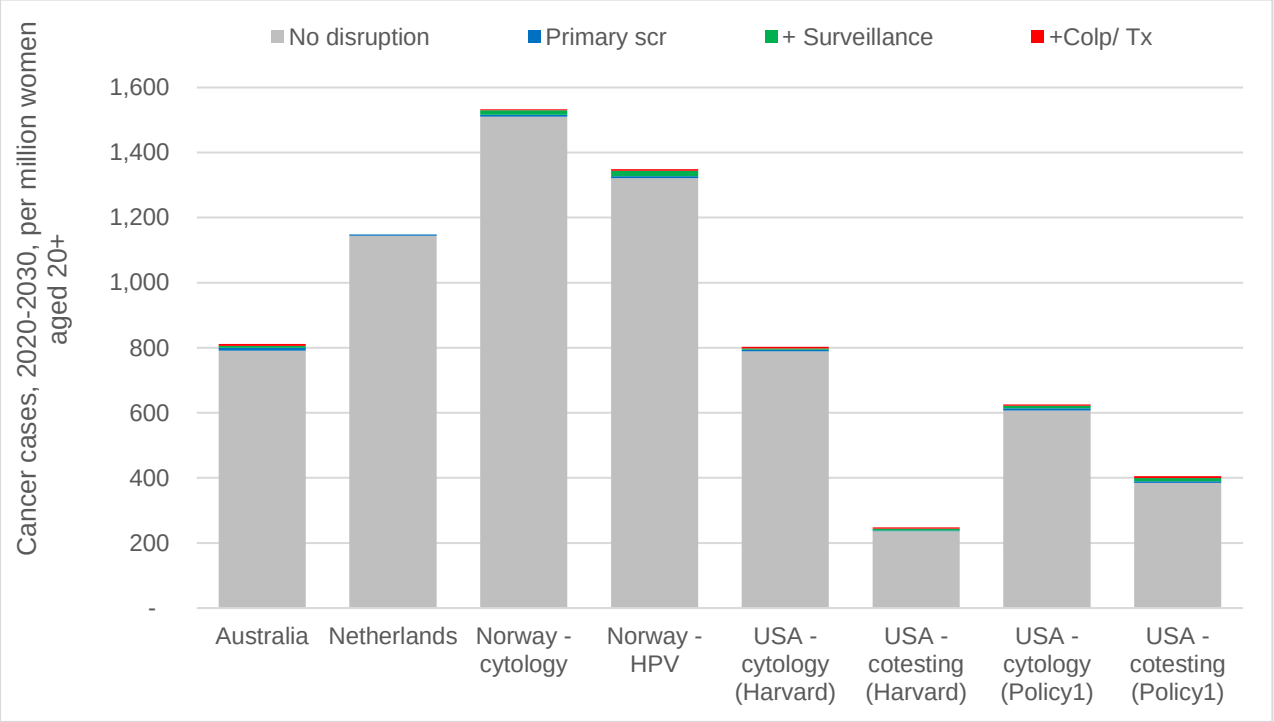
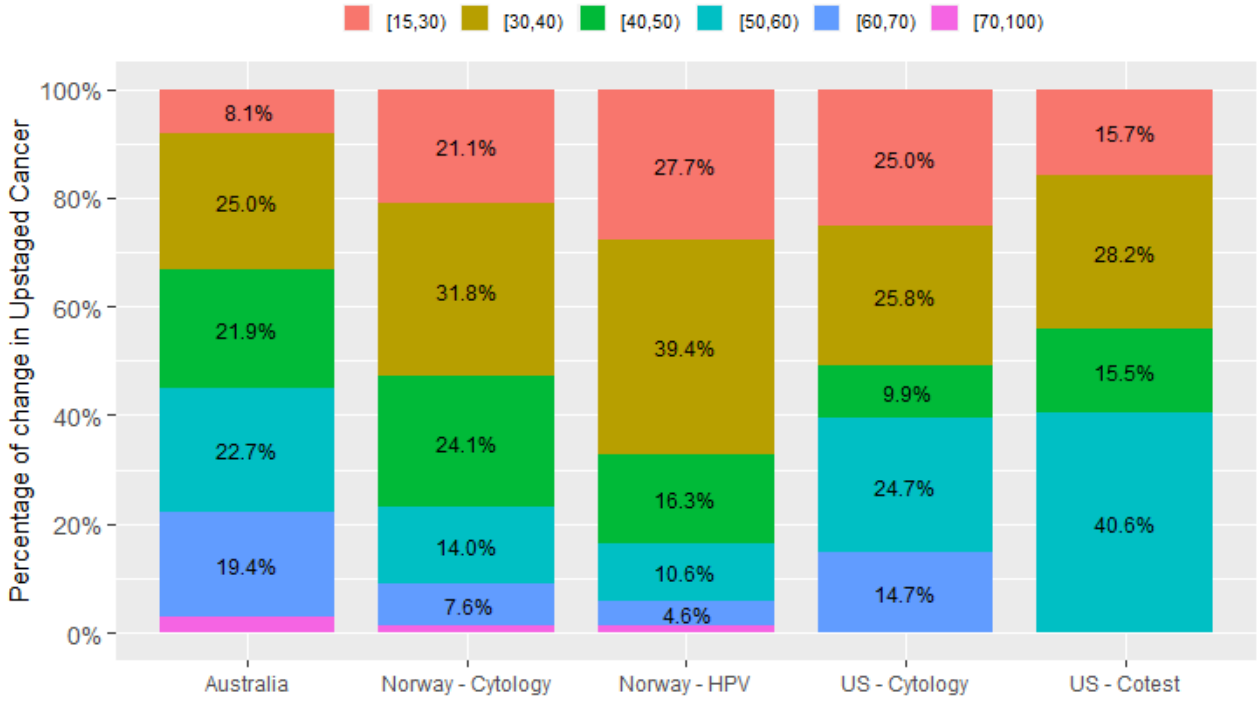
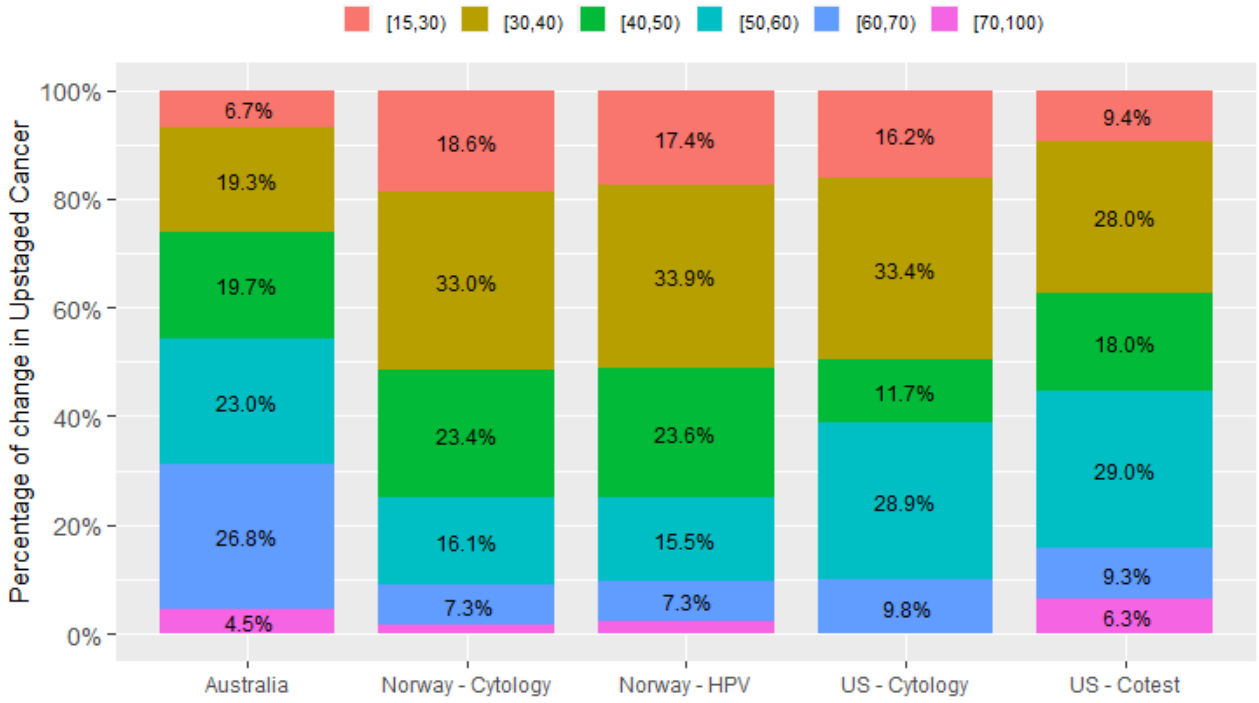


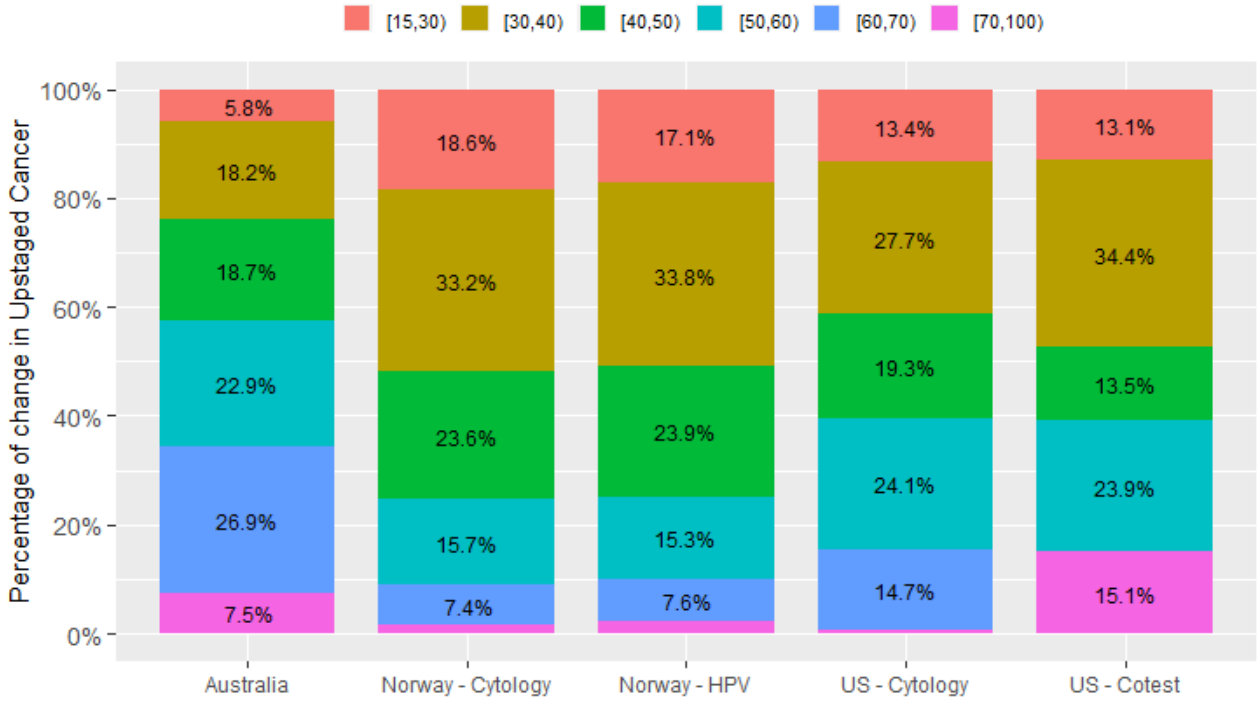
Figure A2 - percentage of upstaged cancer cases over 2020-2030 in each age group*, by setting and extent of disruption (12-month scenarios)
a) primary screening only (S5);



b) primary screening and surveillance visits (S6);



c) screening, surveillance, colposcopy, and precancer treatment (S7) - total

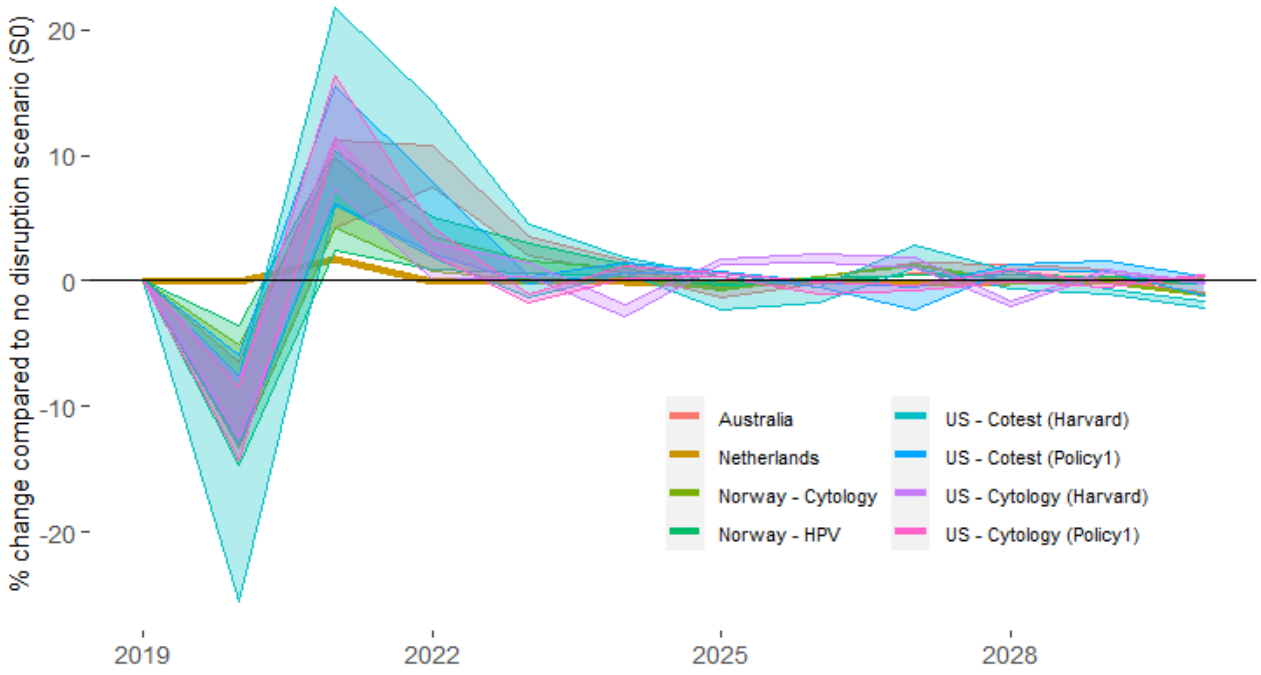


* Age = age in 2020, not necessarily at the time of cancer diagnosis.

Results for the US represent the midpoint of results for the two included models (Harvard and *Policy1-Cervix*).

Figure A3 - percentage change in total cancer cases over 2020-2030, by year and setting: US model results separated

a) 6 months



b) 12 months

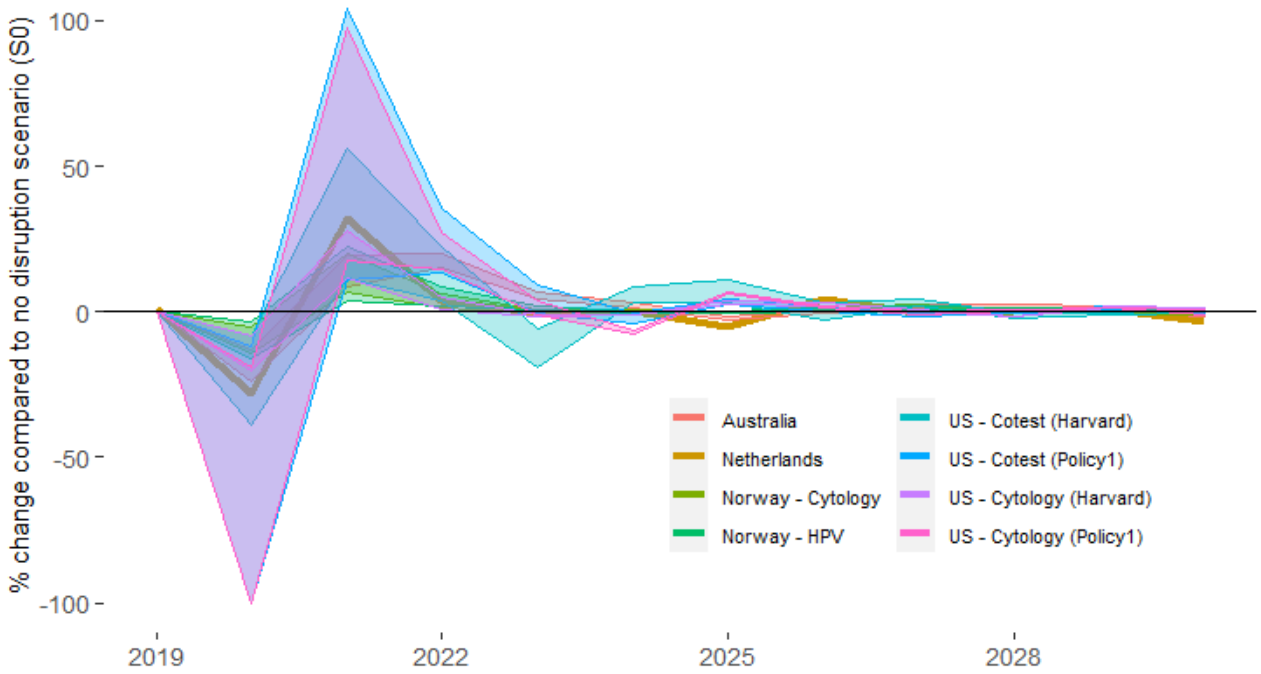
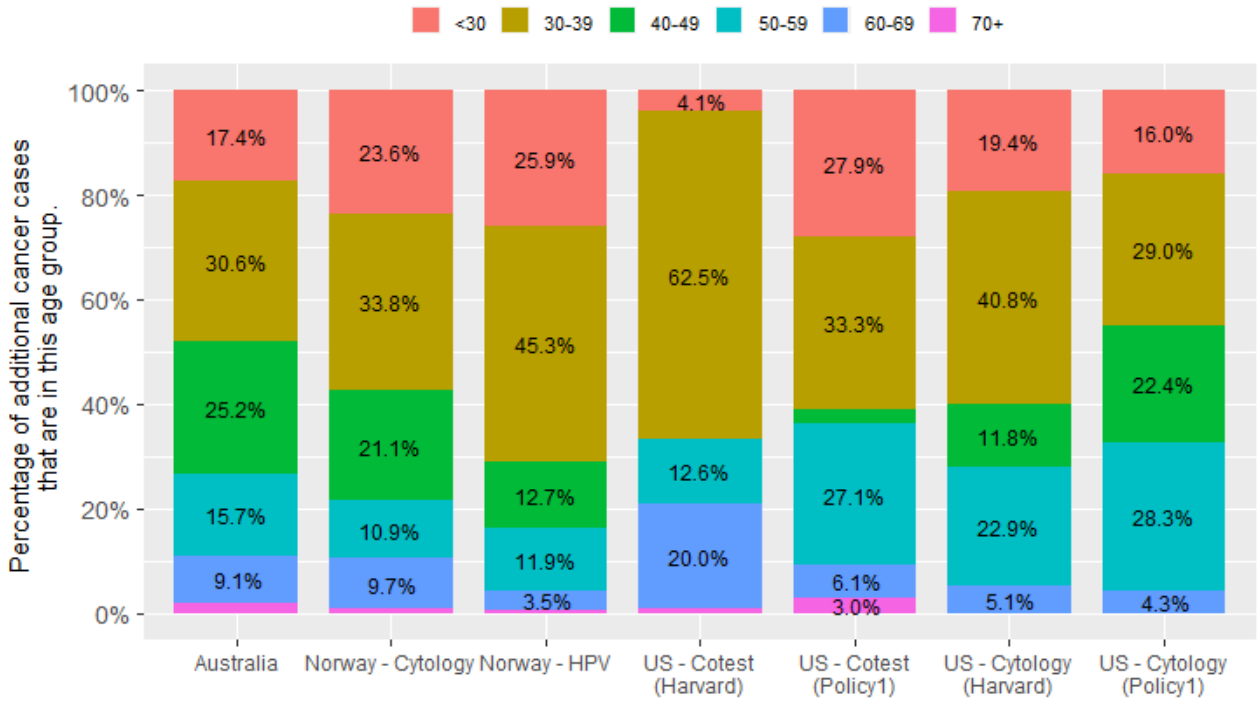
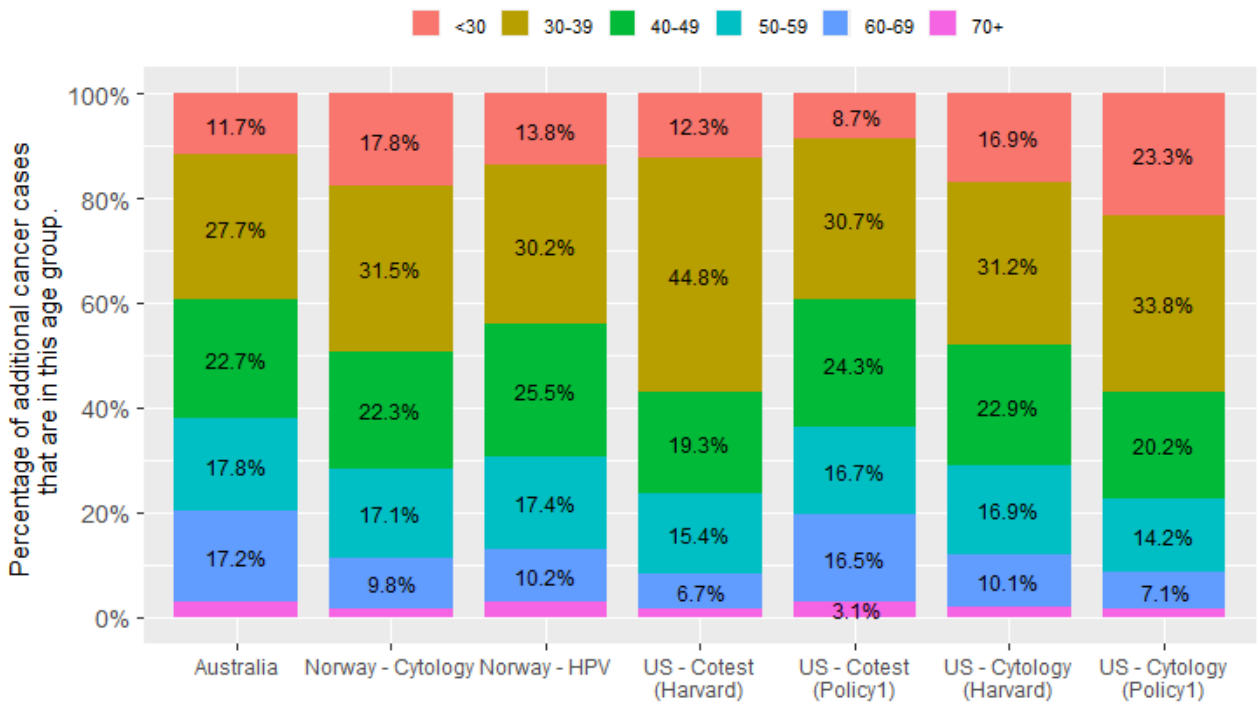


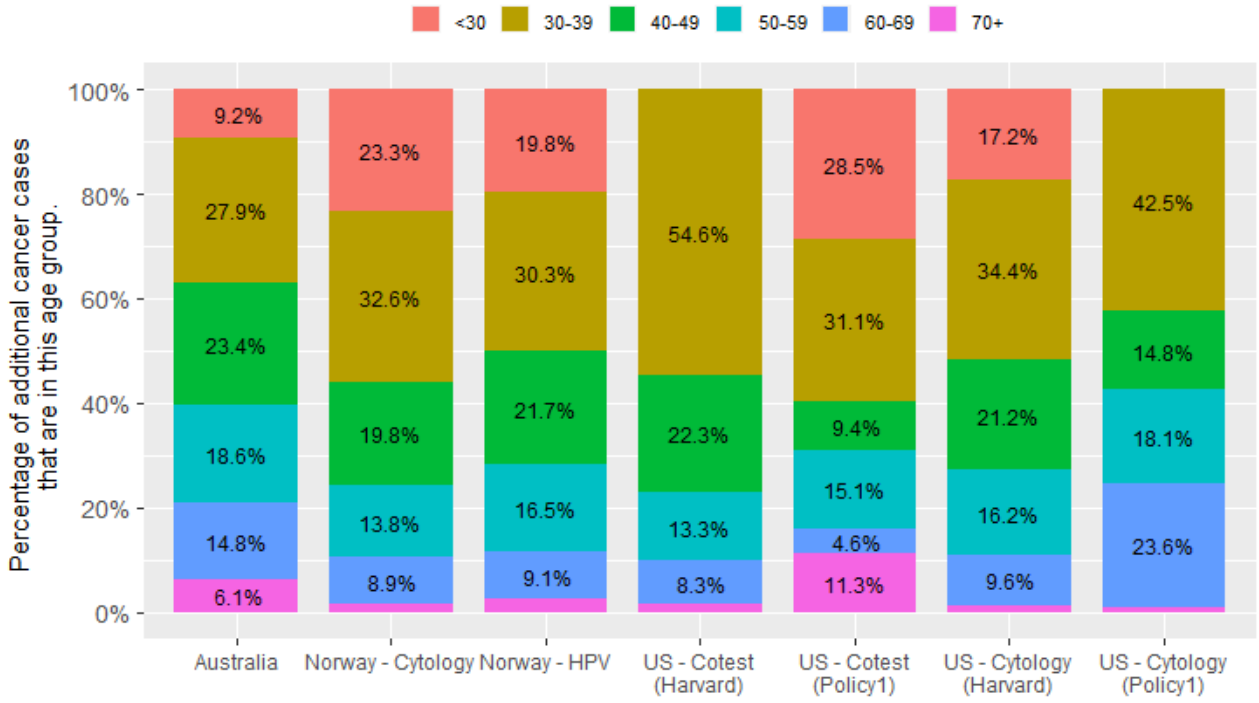
Figure A4 - percentage of additional cancer cases over 2020-2030 in each age group*, by setting and extent of disruption (12-month scenarios): US model results separated
a) primary screening only (S5 compared to S0);



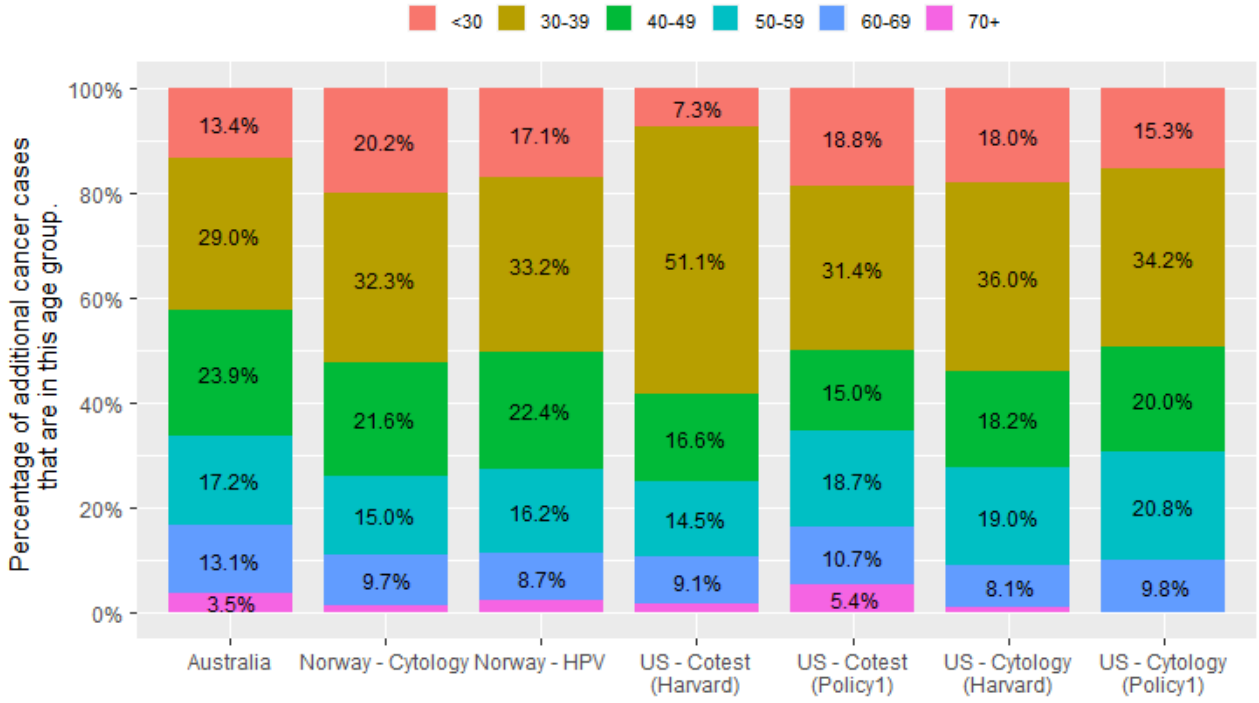
b) surveillance visits (S6 compared to S5);



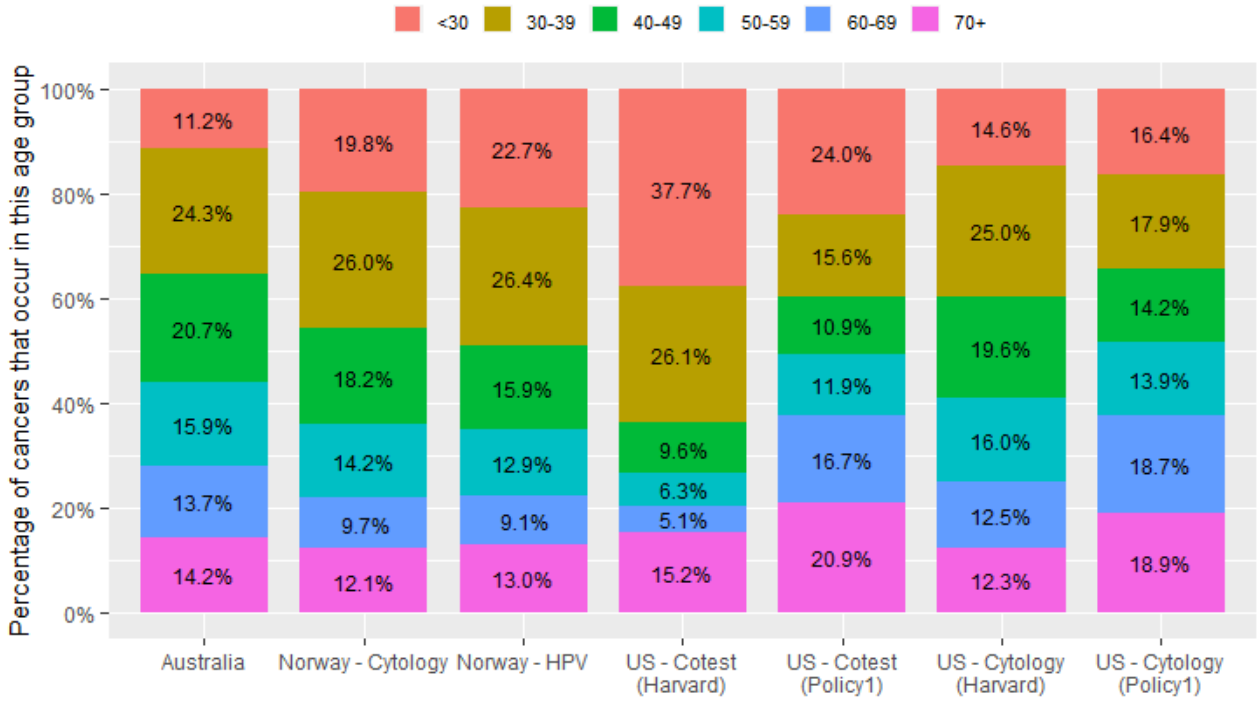
c) colposcopy and precancer treatment (S7 compared to S6);



d) screening, surveillance, colposcopy, and precancer treatment – total (S7 compared to S0)



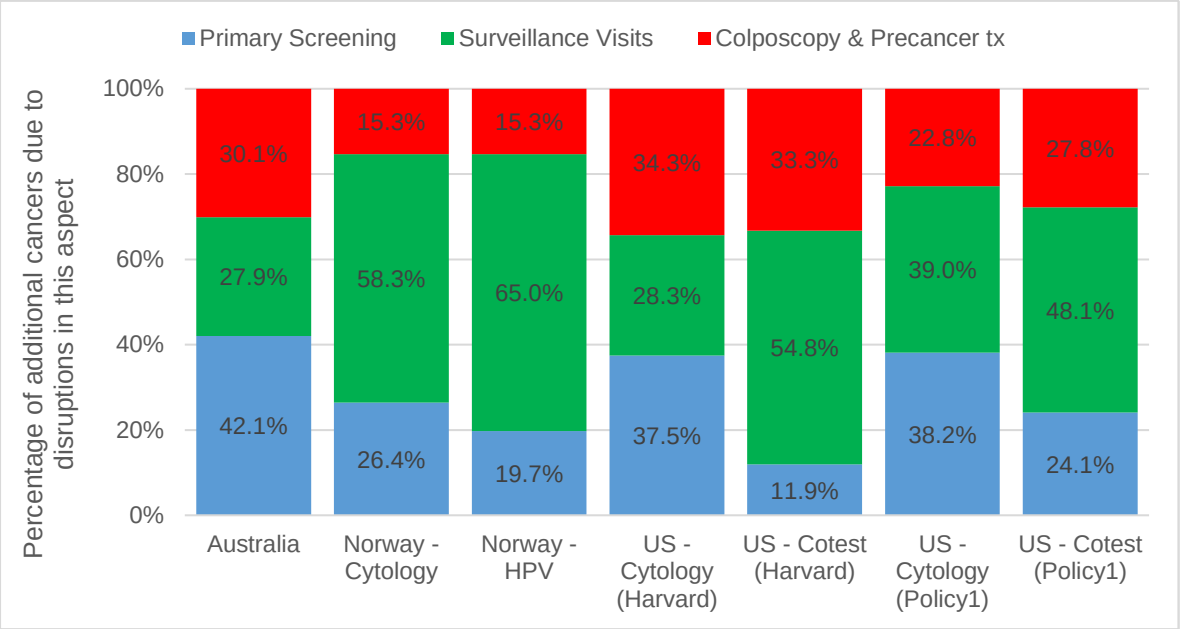
e) expected age distribution in the absence of disruption (S0)



* Age = age in 2020, not necessarily at the time of cancer diagnosis.

Figure A5 - percentage of additional cancer cases and rate of upstaged cancers over 2020-2030 due to type of disruption, by setting and extent of disruption (12-month scenarios): US model results separated

a) additional cancers



b) upstaged cancers

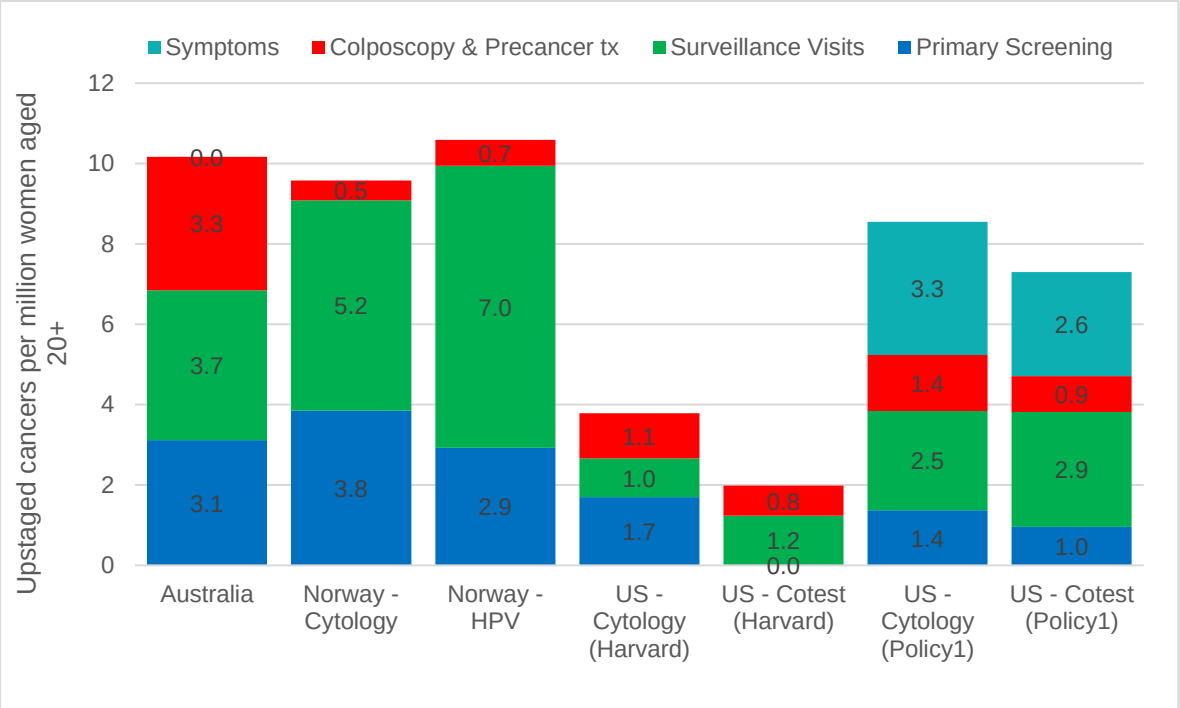
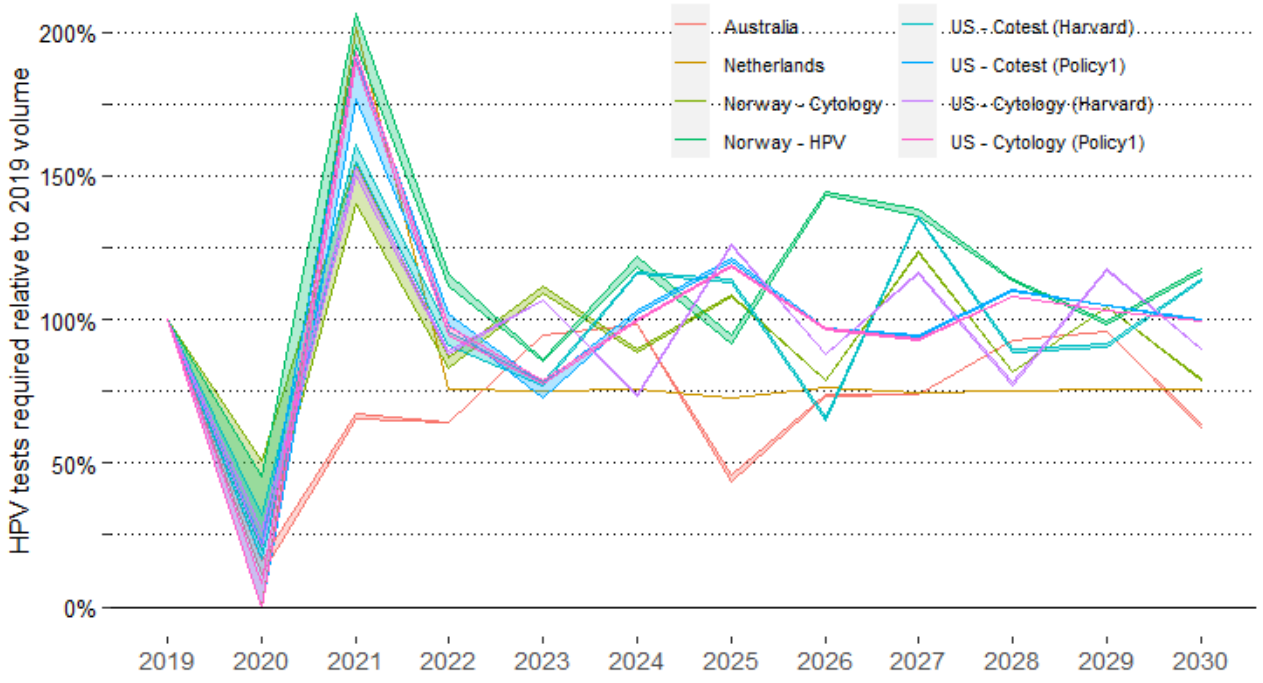


Figure A6 - relative demand for resources over 2020-2030 to achieve the modelled rapid recovery, by year and setting: US model results separated

a) HPV tests



b) colposcopies