HPV Prevention and Control Board

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Technical Meeting: Accelerating HPV-related Cancer Elimination
6-7 June 2024, Antwerp, Belgium

Session 6: Accelerating Elimination of Cervical Cancer: Transforming current insights into equitable strategies for global success

Rethinking Cervical Cancer Elimination Goal Indicators: From Age-Standardized Incidence Rates to Lifetime Risks

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Invited Commentary

Invited Commentary: Rethinking Cervical Cancer Elimination in Terms of Lifetime Risk Rather Than Arbitrarily Defined Age-Standardized Incidence Rates

Talía Malagón* and Eduardo L. Franco

Our commentary in AJE was about:

Vänskä S, Luostarinen T, Lagheden C, Eklund C, Kleppe SN, Andrae B, Sparén P, Sundström K, Lehtinen M, Dillner J. Differing Age-Specific Cervical Cancer Incidence Between Different Types of Human Papillomavirus: Implications for Predicting the Impact of Elimination Programs. Am J Epidemiol. 2021 Apr 6;190(4):506-514.

Age-standardized incidence rates

- Age is a key determinant of the risk of developing cancer; global comparisons of disease occurrence must adjust for age to be meaningful

- **Age-standardized incidence rate** is the yearly rate that would have been observed in a population if it had the age composition of a reference "standard" population

- For historical reasons, the IARC uses the **Segi-Doll world standard population** for age standardization in all publications

Figure: Age-standardized incidence rates of cervical cancer per 100,000 in 2022 (GLOBOCAN 2022)

ASR (World) per 100 000

- 24.6–95.9
- 15.9–24.6
- 12.0–15.9
- 7.1–12.0
- 2.1–7.1

Not applicable
No data
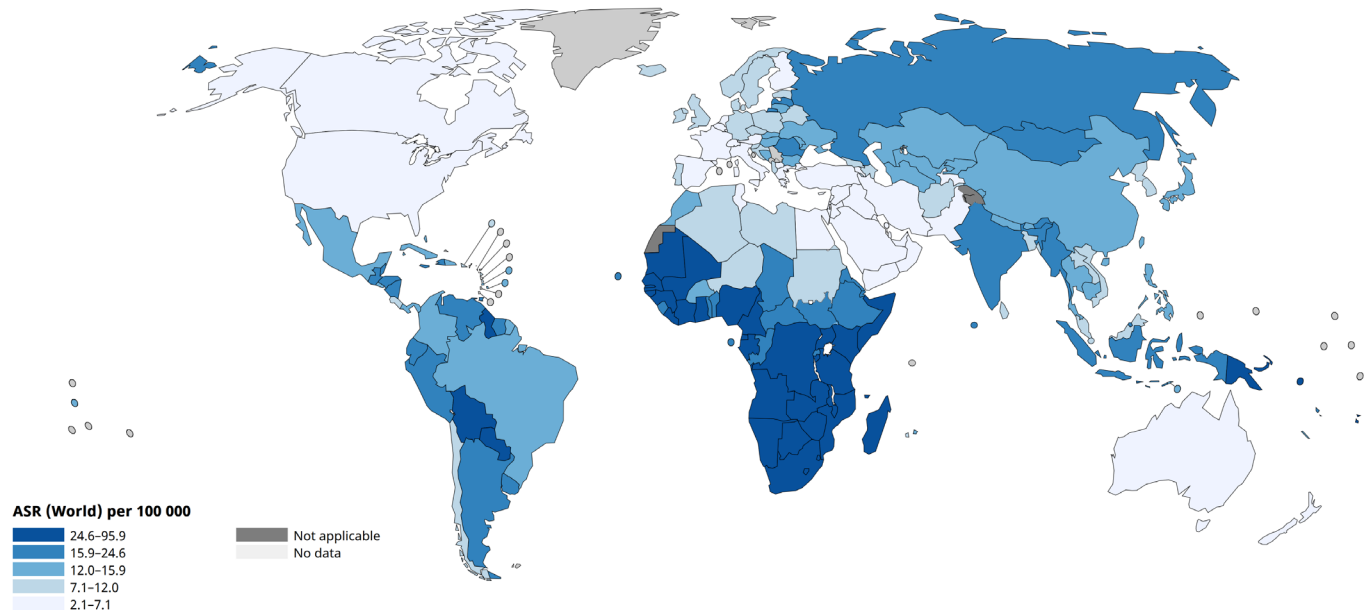
Age structure of developing and developed countries

Age structure varies over **space**
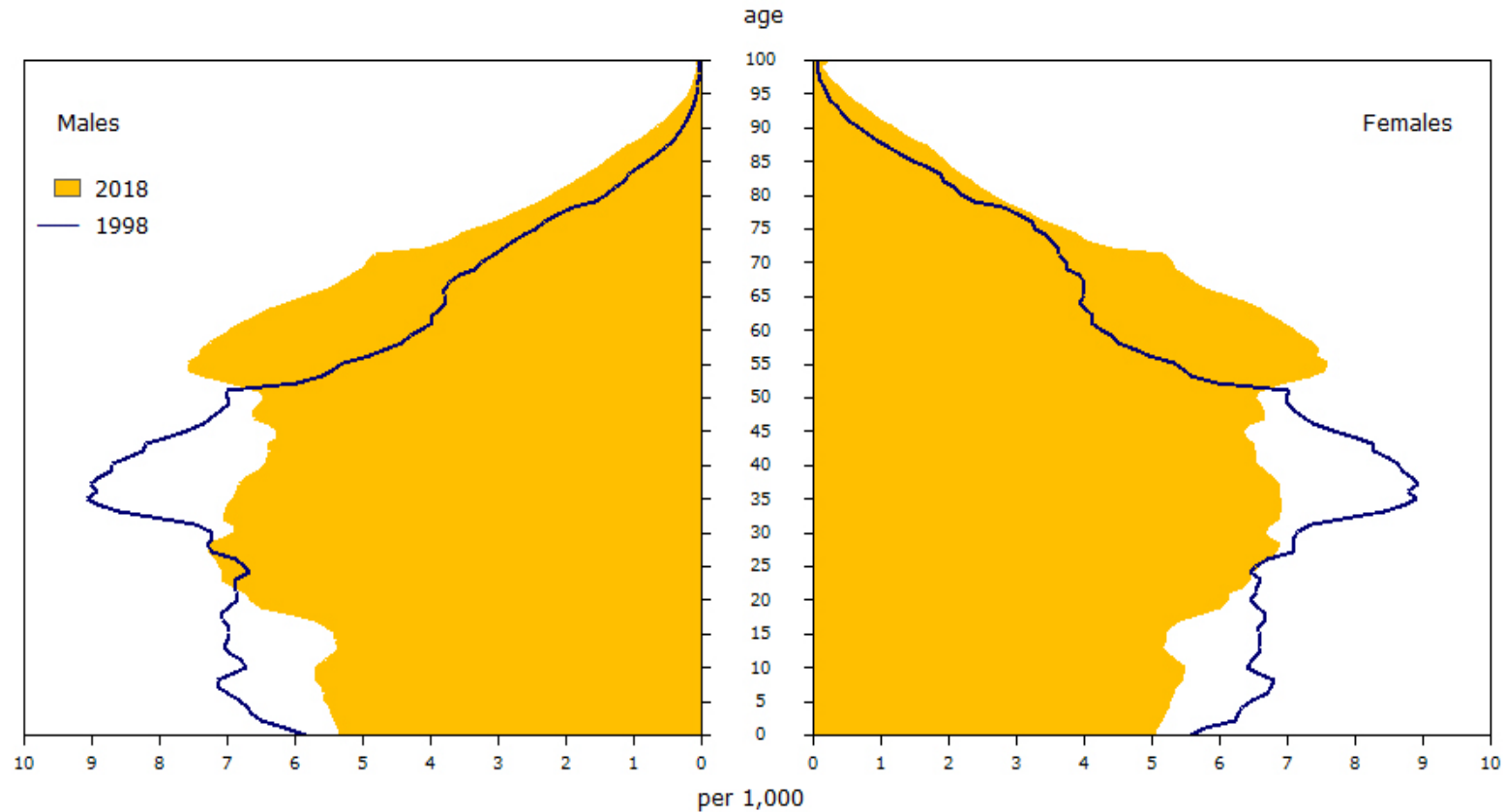
More developed

Less developed
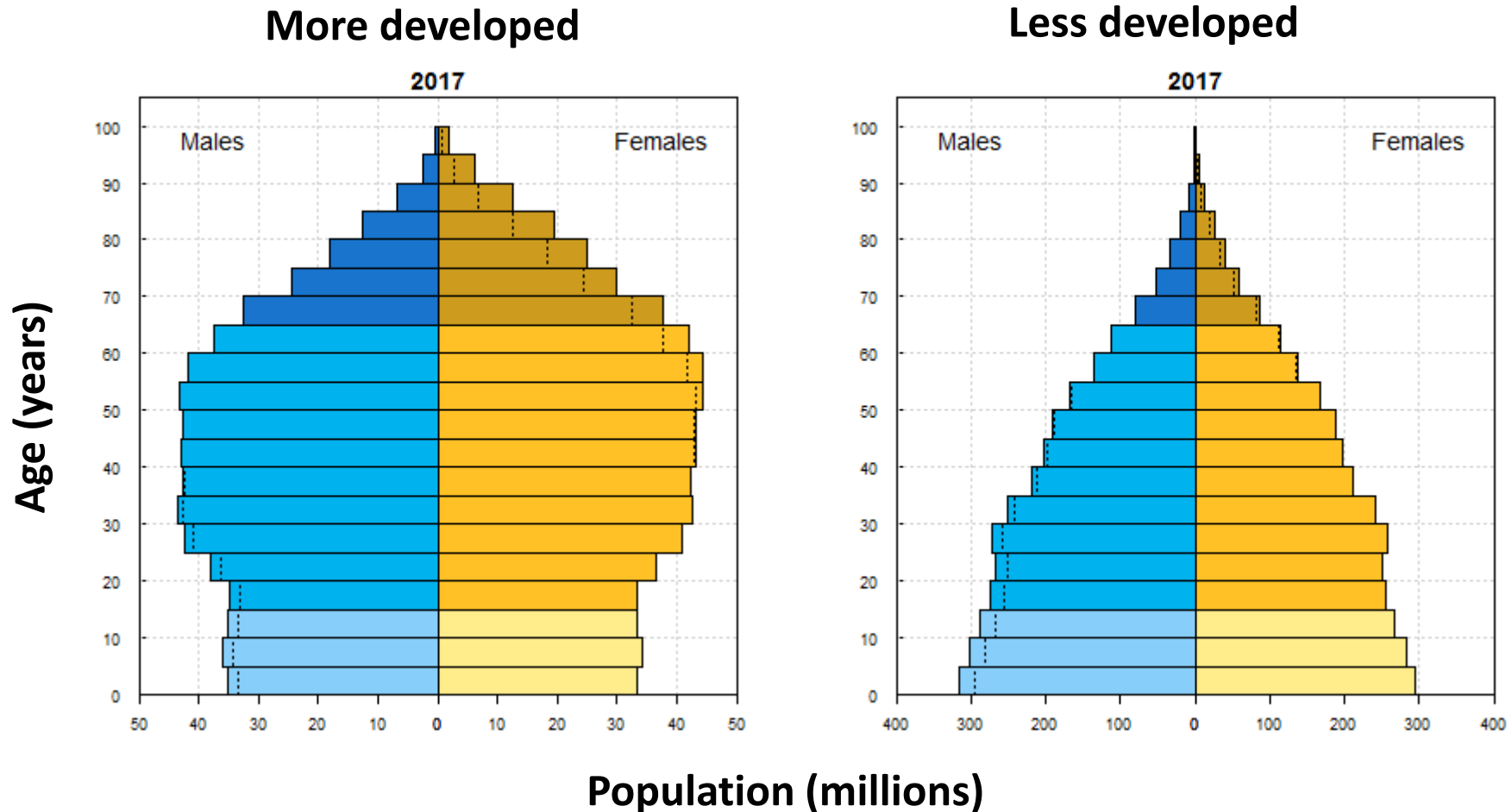
Source: United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision.

Age structure of Canadian population, 1998 and 2018

Age structure varies over **time**

Figure 2.1
Age pyramid of population estimates as of July 1, 1998 and 2018, Canada

Source: Statistics Canada. 2018. *Annual Demographic Estimates: Canada, Provinces and Territories*, Statistics Canada Catalogue no. 91-215-X.

Source populations used for age standardization

Age (years)	World (Segi 1960)	World (WHO) 2000-25*	European (Scandinavian) 1960	US 2000	US 1990	US 1970	US 1950	Canadian 1991	Canadian 1996	Canadian 2011	European 2011-2030
< 1	24,000	17,917	16,000	13,818	12,936	17,151	20,882	14,334	12,342	55,297	50,000
1-4	96,000	70,652	64,000	55,317	60,863	67,265	86,376	55,131	53,893		
5-9	100,000	86,870	70,000	72,533	72,772	98,204	87,591	69,454	67,985	52,717	55,000
10-14	90,000	85,970	70,000	73,032	68,812	102,304	73,785	68,034	67,716	55,853	55,000
15-19	90,000	84,670	70,000	72,169	71,384	93,845	70,450	68,495	67,841	65,194	55,000
20-24	80,000	82,171	70,000	66,478	76,476	80,561	76,191	75,016	67,761	68,555	60,000
25-29	80,000	79,272	70,000	64,529	85,694	66,320	81,237	89,944	72,914	69,006	60,000
30-34	60,000	76,073	70,000	71,044	87,905	56,249	76,425	92,400	87,030	67,786	65,000
35-39	60,000	71,475	70,000	80,762	80,267	54,656	74,629	83,388	88,510	66,188	70,000
40-44	60,000	65,877	70,000	81,851	70,829	58,958	67,712	76,063	80,055	69,474	70,000
45-49	60,000	60,379	70,000	72,118	55,778	59,622	60,190	59,536	71,847	79,199	70,000
50-54	50,000	53,681	70,000	62,716	45,638	54,643	54,893	47,649	55,812	78,365	70,000
55-59	40,000	45,484	60,000	48,454	42,345	49,077	48,011	44,041	44,869	68,518	65,000
60-64	40,000	37,187	50,000	38,793	42,685	42,403	40,210	42,326	40,705	59,705	60,000
65-69	30,000	29,590	40,000	34,264	40,657	34,406	33,199	38,570	37,858	44,636	55,000
70-74	20,000	22,092	30,000	31,773	32,145	26,789	22,641	29,660	32,589	33,597	50,000
75-79	10,000	15,195	20,000	26,999	24,612	18,871	14,283	22,127	23,232	26,769	40,000
80-84	5,000	9,097	10,000	17,842	15,817	11,241	7,467	13,595	15,424	20,416	25,000
85-89	5,000	4,398	10,000	15,508	12,385	7,435	3,828	10,237	11,617	12,426	15,000
90-94		1,500								6,299	10,000
95-99		400									
100+		50									
Total	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000

Source: Ahmad et al., Age standardization or rates: a new WHO standard. GPE Discussion Paper Series No. 31. EIP/GPE/EBD WHO 2001
https://seer.cancer.gov/stdpopulations/single_age.html . Canadian Cancer Statistics, 2017 and previous ones
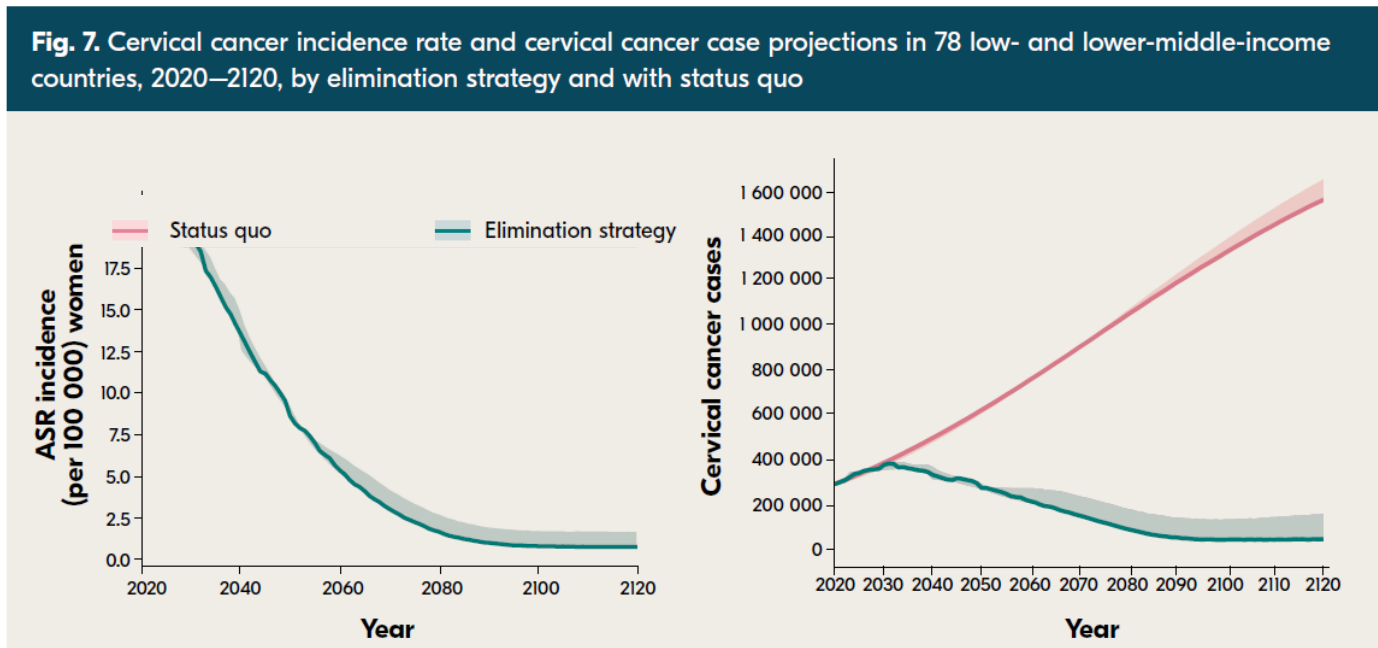
Beware of biases: Effect of Choice of Standard Population for Age-adjustment

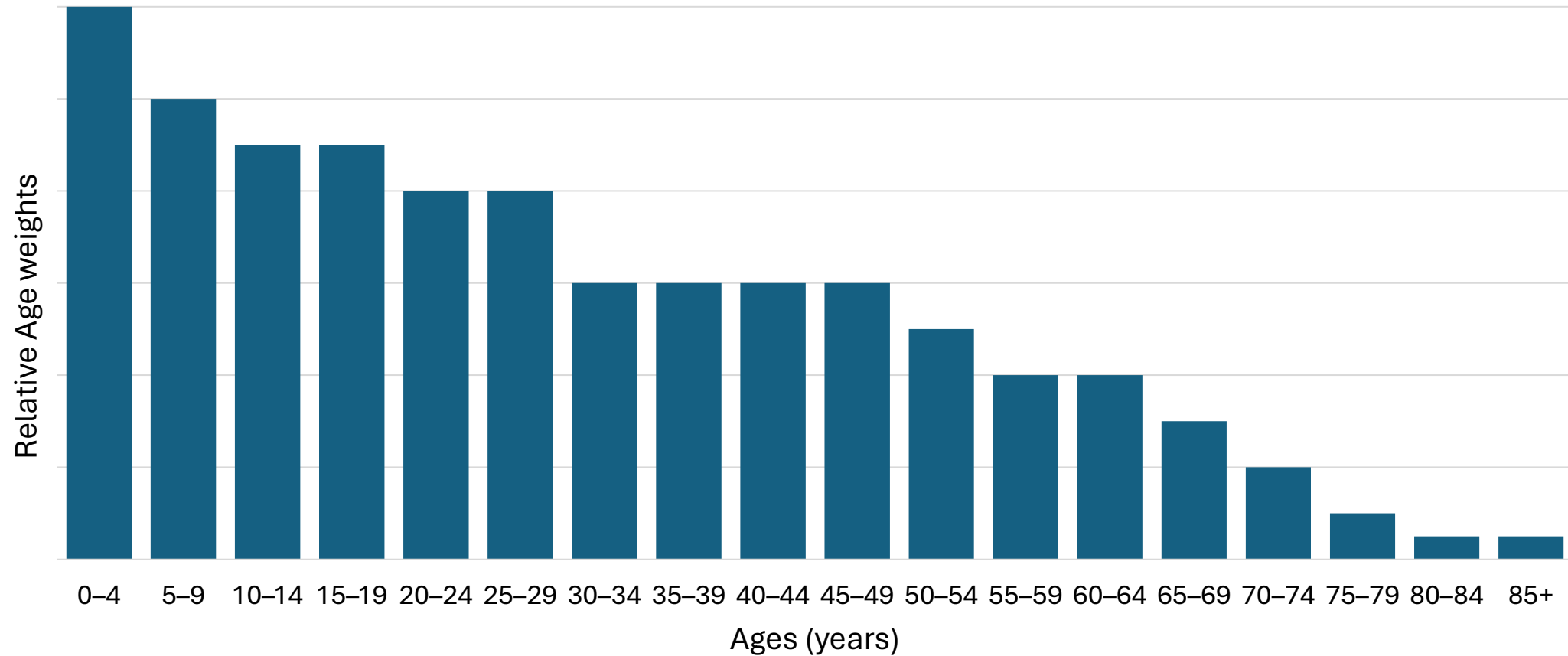| Gender	Cancer Site	Rate according to standard population		Difference (US-World)
		US 2000	World 1960	
Males	Prostate	177.6	117.7	50.9%
	Lung	82.1	51.5	59.4%
	Testis	5.6	5.1	9.8%
Female	Breast	137.1	99.0	38.6%
	Cervix	8.0	6.3	27.1%
	Vulva	2.4	1.5	56.7%

Average age-adjusted incidence rates per 100,000 (1998-2002) in the US SEER program

WHO Global Strategy for cervical cancer elimination

- All countries must reach and maintain an **age-standardized** incidence rate of below 4 cervical cancers per 100 000 women per year.

- This elimination threshold was selected by the WHO as it was deemed achievable based on **expert consultations** and modeling

- Implicitly, this elimination threshold is also based on the Segi-Doll world standard population

Fig. 7. Cervical cancer incidence rate and cervical cancer case projections in 78 low- and lower-middle-income countries, 2020—2120, by elimination strategy and with status quo

World Health Organization 2020
https://www.who.int/publications/i/item/9789240014107

Segi-Doll standard world population age distribution Weights

Choice of standard population

- IARC has previously argued that while the Segi-Doll standard is outdated, the choice of standard is arbitrary and does not matter as its main function is to enable comparisons between countries and across time

- However, an age-standardized rate as a public health target is a new function where the age weights ARE important because **the age weights represent a value judgement about the importance of preventing a cancer at that age**

- Does the Segi-Doll world population reflect the public health goal we are aspiring to achieve?

Who and what interventions does the Segi-Doll standard prioritize?

Over 50% of Segi-Doll age weight is in ages <30y. These represent less than 10% of cervical cancers worldwide. Cancers at these ages can only be prevented by vaccination, will not be impacted by screening.


Segi-Doll World Standard

Cervical cancer incidence rate by age (World)
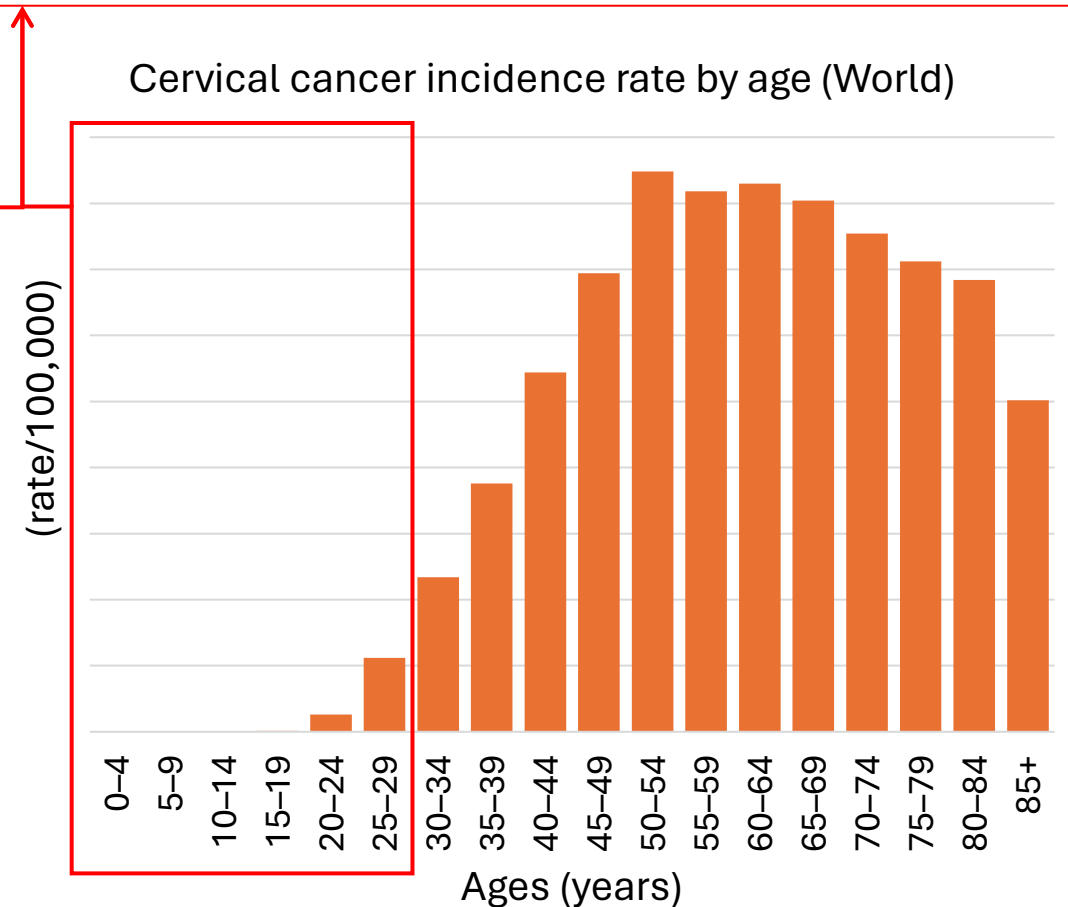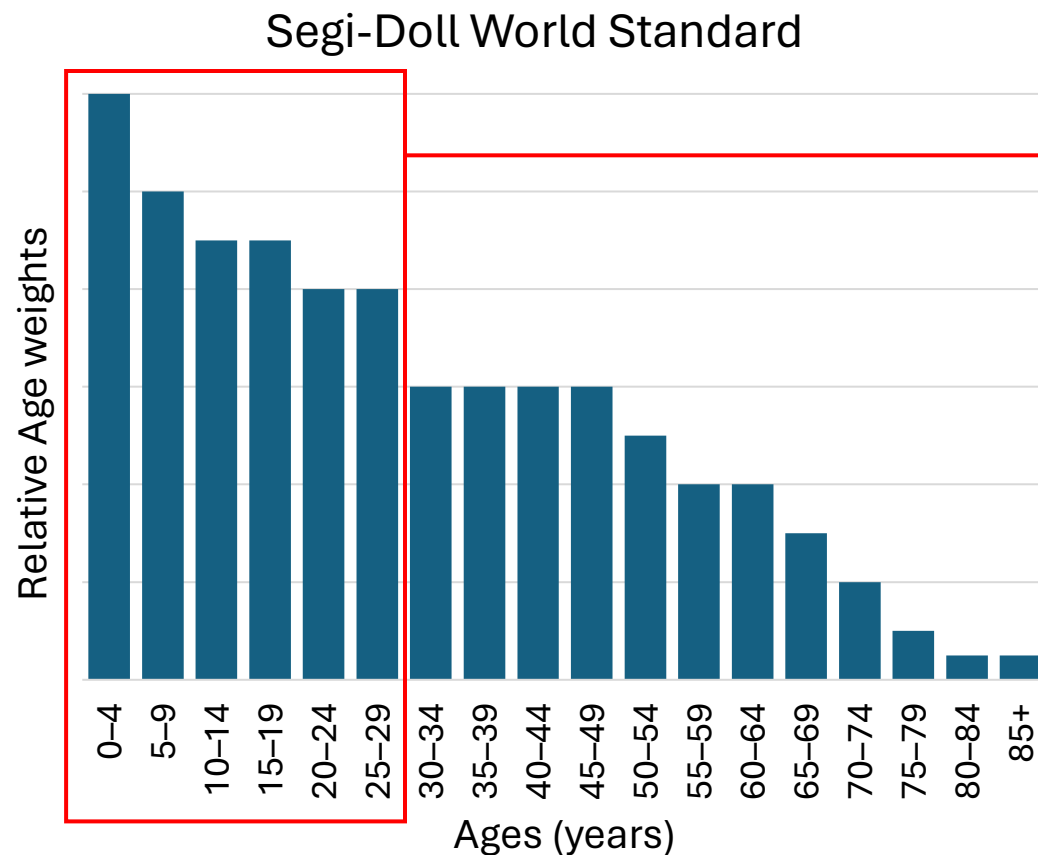
Who and what interventions does the Segi-Doll standard prioritize?

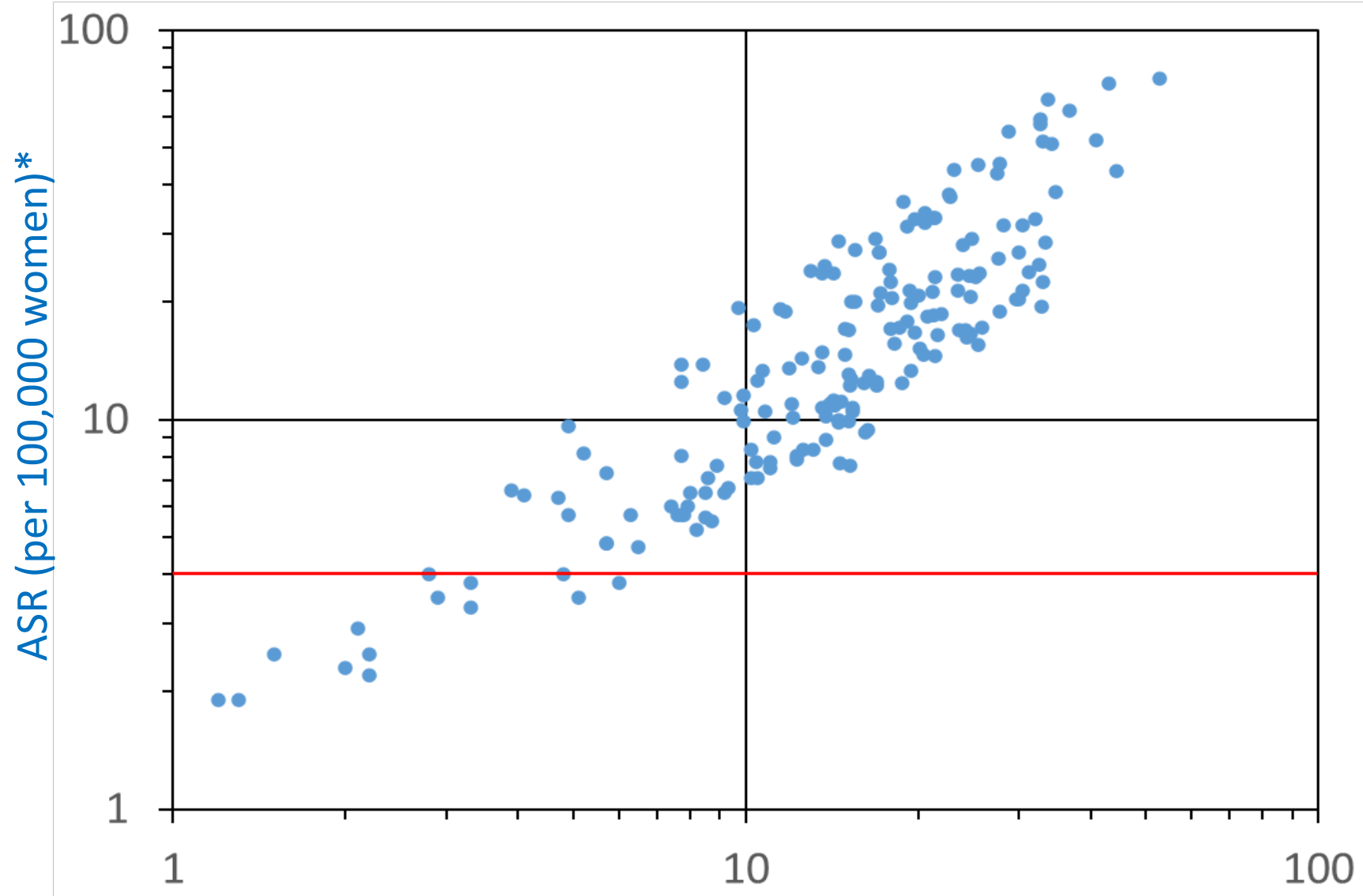Odds ratio: (50/50)/(10/90) = 9

DO WE VALUE PREVENTING CANCERS IN WOMEN <30Y NINE TIMES MORE THAN PREVENTING CANCERS IN WOMEN >30Y?

This is a value judgement that should be made explicit to assess whether target is congruent with societal values.
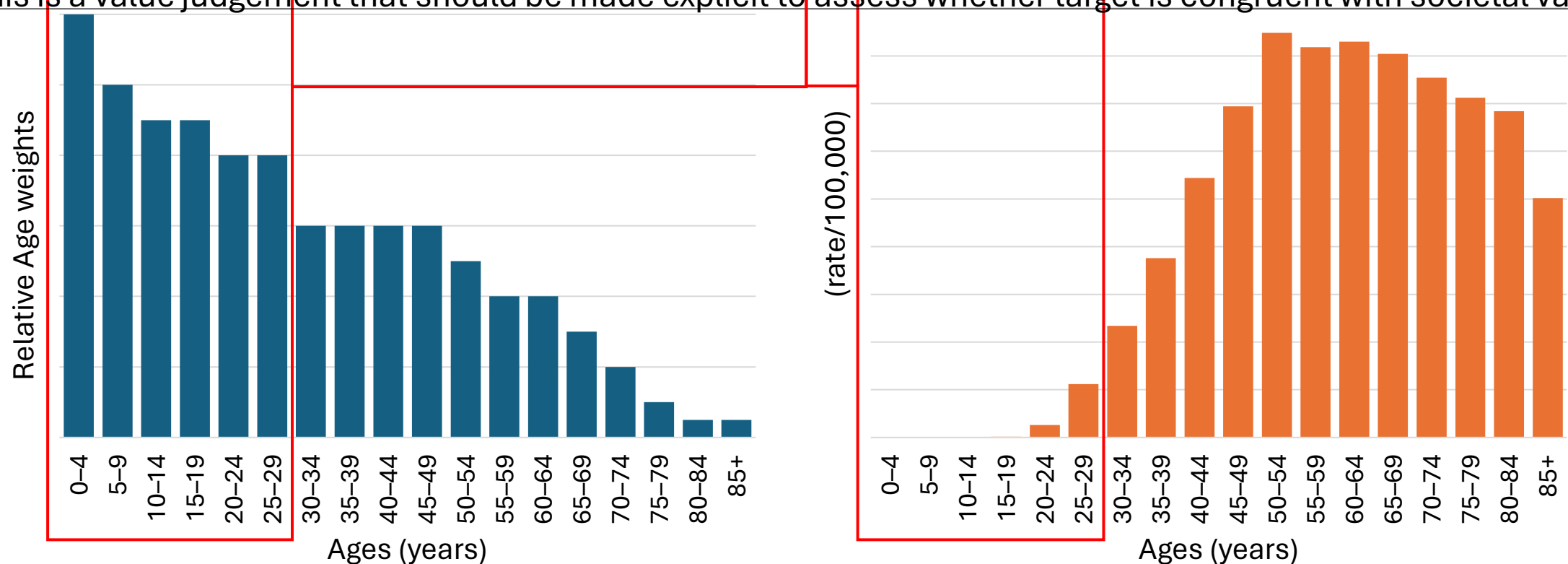
Correlation between crude and age-standardized incidence rate of cervical cancer (GLOBOCAN 2018)

ASR (per 100,000 women)*

Crude rate (per 100,000 women)

* Segi-Doll Standard Population 1960

Relation between ASR and the difference between crude and ASR of cervical cancer (GLOBOCAN 2018)

Crude rate minus ASR

ASR (per 100,000 women)*
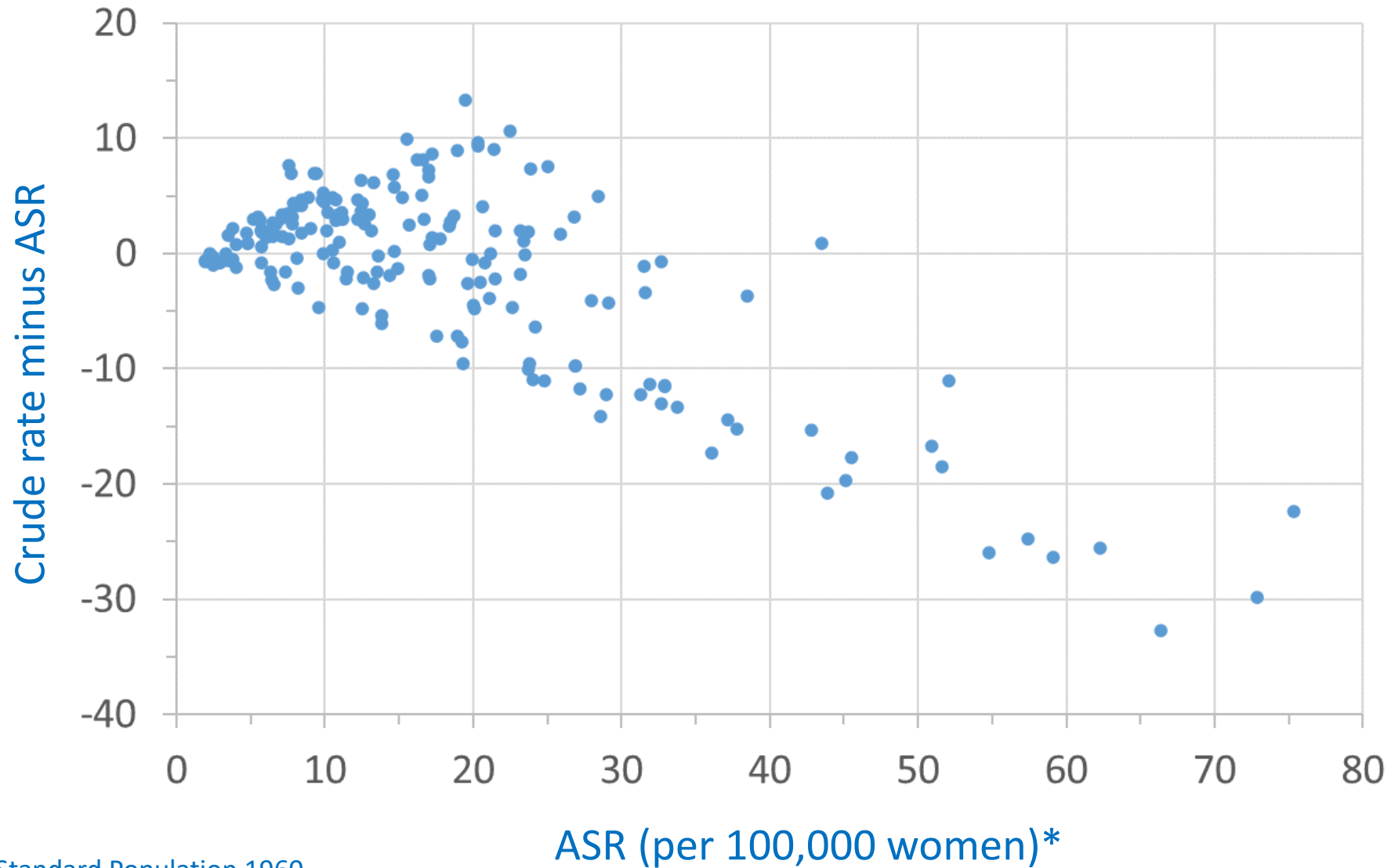
* Segi-Doll Standard Population 1960

Life expectancy

- Life expectancy at birth is the average age a newborn can expect to live if current death rates do not change.

- Life tables provide natural weights proportional to probability of experiencing a health outcome during an average lifetime

Global life expectancy (females) – Proportion remaining alive in cohort of 100,000

Life expectancy 76

https://www.who.int/data/gho/data/indicators
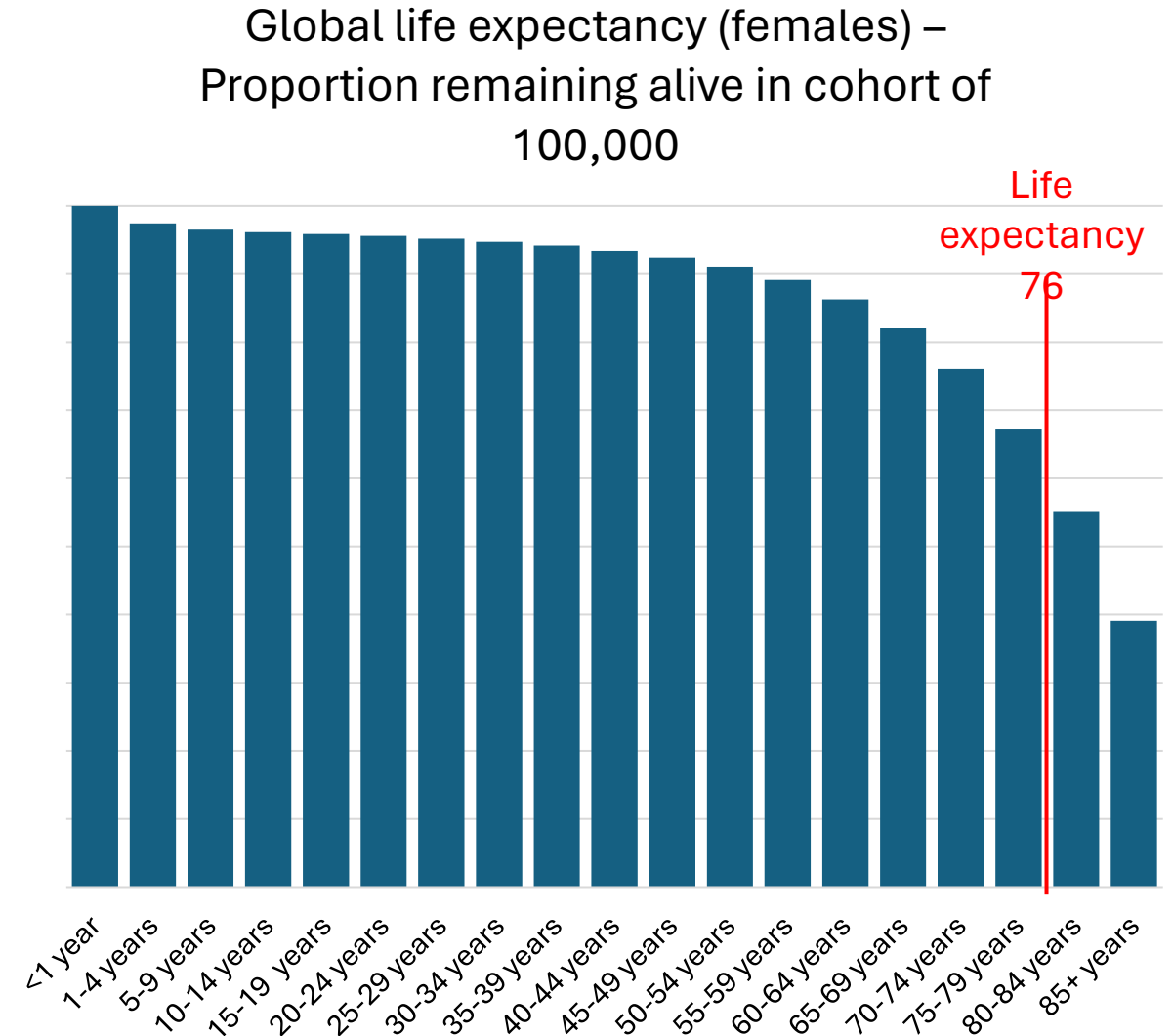
Cumulative lifetime cancer risk

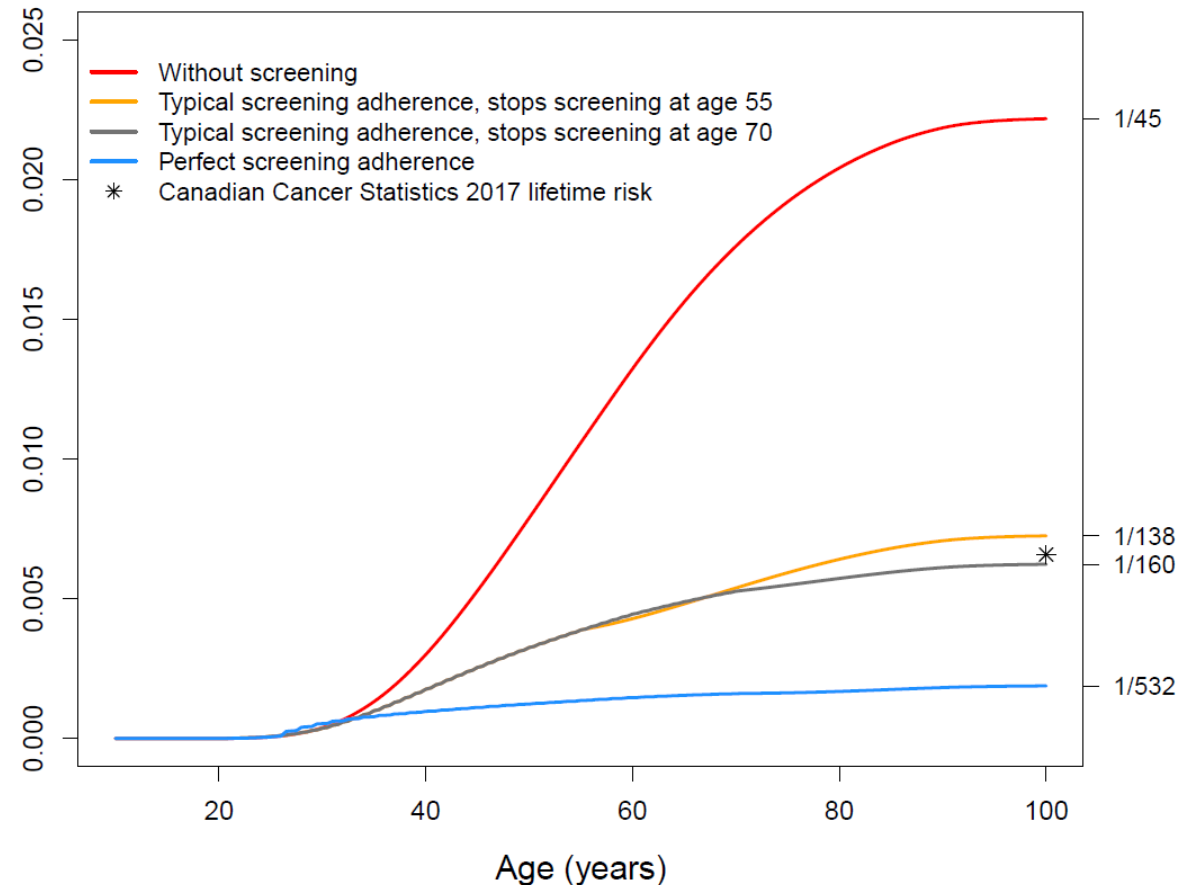- Cumulative lifetime risk of cancer is the probability of experiencing cancer within a lifetime given life expectancy and cancer incidence rates

- Can be age-standardized to a "standard" life expectancy to adjust for differences in life expectancy by country

- Alternative metric to age-standardized cancer incidence rates that has more intuitive appeal

Cumulative lifetime risk of cervical cancer in Canada

Legend:
- Without screening
- Typical screening adherence, stops screening at age 55
- Typical screening adherence, stops screening at age 70
- Perfect screening adherence
- * Canadian Cancer Statistics 2017 lifetime risk

Right axis labels: 1/45, 1/138, 1/160, 1/532

X-axis: Age (years)

Malagón T, Kulasingam S, Mayrand MH, Ogilvie G, Smith L, Bouchard C, Gotlieb W, Franco EL. Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated women: a modelling study. Lancet Oncol. 2018 Dec;19(12):1569-1578.

Standardized lifetime risk in Sweden

- Vänskä et al. (2020) calculated standardized lifetime risks of cervical cancer in Sweden by HPV type using Swedish life expectancy in 2002-2011:
    - Life expectancy in Sweden was 83.1 for females
    - The standardized lifetime risk for HPV-positive cervical cancer was 651 per 100,000 female births (1 in 154 women).
    - The standardized lifetime risk of HPV-negative cervical cancer was 109 per 100,000 female births (1 in 917 women).
    - While not estimated in article, other data sources suggest lifetime risk without vaccination or screening would be around 1 in 30-60 women.

- Assuming perfect vaccination and screening would prevent all HPV-positive cancers, effectively cervical cancer lifetime risk could be theoretically reduced to 1 in 917 women using current interventions.

Vänskä S, Luostarinen T, Lagheden C, Eklund C, Kleppe SN, Andrae B, Sparén P, Sundström K, Lehtinen M, Dillner J. Differing Age-Specific Cervical Cancer Incidence Between Different Types of Human Papillomavirus: Implications for Predicting the Impact of Elimination Programs. Am J Epidemiol. 2021;190(4):506-514.

Why standardized lifetime risks?

- It is more straightforward and less age-discriminatory to define an **ideal life expectancy** than an **ideal age distribution** for age weights.
  - Lifecourse approach
  - Age weights correspond to the probability that cervical cancer would impact a woman and prevent her from pursuing other opportunities within a "standard" lifetime
- The "standard" lifetime could be based on observed maximal life expectancy
  - DALYs use standard female life expectancy of 82.5 years
  - WHO projections suggest female life expectancy may rise to 91.3 within next century

Takeaways

- Cervical cancer elimination targets make implicit value judgements about age and the value of prevention at different ages that should be explicit

- The WHO target incidence rate of <4 per 100,000 uses age weights that places significantly higher value on preventing cancers in women <30y.

- Alternative standard age weights might be more aligned with societal values

- We propose that a standardized lifetime risk under maximum life expectancy would be a more attractive elimination target due to its age weights, which are proportional to expected benefit of prevention in terms of life years gained

- Data from Sweden suggests an aspirational elimination target could be to reduce the standardized lifetime risk to around 1 in 917 women.