Published in final edited form as:

Ann Intern Med. 2014 July 15; 161(2): 104–112. doi:10.7326/M13-2867.

Personalizing Age of Cancer Screening Cessation Based on Comorbidity: Model estimates of harms and benefits

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Abstract

Background—Harms and benefits of cancer screening depend on age and comorbidity, yet reliable estimates are lacking.

Objective—To estimate the harms and benefits of cancer screening by age and comorbidity to inform decisions about screening cessation.

Design—Collaborative modeling with seven well-established cancer simulation models and common data on average and comorbidity level-specific life expectancy from SEER-Medicare.

Setting—US population.

Patients—US cohorts aged 66–90 years in 2010 with average health or one of four comorbidity levels (linked to specific conditions): none, mild, moderate, or severe.

Intervention—Mammography, prostate-specific antigen testing, or fecal immunochemical testing.

Measurements—Lifetime cancer deaths prevented and life-years gained (benefits); false-positive tests and overdiagnosed cancers (harms). For each comorbidity level: the age at which harms and benefits of screening were similar to that for individuals with average health undergoing screening at age 74.

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Results—Screening 1000 women with average life expectancy at age 74 for breast cancer resulted in 79–96 (range across models) false-positives, 0.5–0.8 overdiagnosed cancers, and 0.7–0.9 breast cancer deaths prevented. While absolute numbers of harms and benefits differed across cancer sites, the ages at which to cease screening were highly consistent across models and cancer sites when based on harm-benefit ratios comparable to screening average-health individuals at age 74. For individuals with no, mild, moderate, and severe comorbidities, screening until ages of 76, 74, 72, and 66, respectively, resulted in similar harms and benefits as for average-health individuals.

Limitations—Comorbidity only influenced life expectancy.

Conclusion—Comorbidity is an important determinant of harms and benefits of screening. Estimates of screening benefits and harms by comorbidity can inform discussions between providers and their older patients about personalizing decisions about when to stop cancer screening.

Primary Funding Source—National Cancer Institute at the National Institutes of Health

INTRODUCTION

The US Preventive Services Task Force (USPSTF) in 2008 recommended against routine breast and colorectal cancer screening after age 74 (1, 2) because the average gain in life-years associated with extending screening beyond age 74 was felt to be small in comparison to the harms. However, since comorbidity might shift the balance of harms and benefits towards cessation at younger or older ages than 74, the USPSTF and other groups recommended that screening cessation decisions be individualized based on health status (1–4).

There are over 13 million individuals between ages 75 and 85 in the US, and this number is expected to increase to more than 28 million by 2050 (5). Thus, clinicians will be caring for a large and growing number of individuals affected by the uncertainty in how to assess health status and make recommendations regarding screening upper age limits. There is considerable heterogeneity in the health of these older individuals, yet none of the current guidelines provide clinicians with data to implement personalized approaches. Previous decision analyses looking at health benefits of different cancer screening cessation ages by life expectancy (6, 7) have limited clinical utility because they did not provide a framework for determining life expectancy.

To fill this gap, we estimated the harms and benefits of breast, prostate, and colorectal cancer screening by age based on individual comorbidity using 7 established, independently developed models from the Cancer Intervention and Surveillance Modeling Network (CISNET).

METHODS

We used microsimulation models to estimate the harms and benefits of attending one more cancer screen in regularly screened cohorts aged 66–90 by comorbidity level. The harms and

benefits for each cohort were compared to that of an average-health cohort attending one more screen at age 74.

The Models

The models used for this analysis are MISCAN-Fadia (Microsimulation SCreening Analysis – Fatal diameter) and G-E model (Georgetown-Einstein) for breast cancer;(8, 9) MISCAN-prostate and the FHCRC (Fred Hutchinson Cancer Research Center) model for prostate cancer;(10, 11) and MISCAN-Colon, CRC-SPIN (ColoRectal Cancer Simulated Population model for Incidence and Natural history), and SimCRC (Simulating ColoRectal Cancer) for colorectal cancer (12–14). Each model simulates the life histories of individuals from birth to death and tracks underlying disease in the presence and absence of screening. These models have previously been applied to inform the USPSTF recommendations for breast and colorectal cancer screening (15, 16) and to evaluate prostate cancer screening and treatment interventions (17, 18). Using multiple models per cancer site provides a credible range of results and serves as a sensitivity analysis on the impact of variations in underlying model structure and assumptions (Appendix Table 1). Briefly, screening extends life through detection of disease at an earlier stage or a smaller size when it may have better survival after treatment than in the absence of screening. Inputs were standardized across models within cancer site, including test characteristics, screening and follow-up assumptions, treatment distributions, and cancer-specific and other-cause survival. Sources for the model inputs have been described in prior publications (15, 16, 19). Descriptions of each model have been published elsewhere (8–14); model profiles are available (<http://cisnet.cancer.gov/profiles/>) and additional information about the models is available from the authors upon request. CISNET also includes procedures for external collaboration for interested investigators (<http://cisnet.cancer.gov>). Selected model outputs for 74-year old individuals who have average health (and life expectancy) and who had been screened regularly prior to age 74 are provided in Table 1.

Population—After assuming that all individuals underwent regular screening starting at age 50 with biennial mammography, biennial prostate-specific antigen (PSA) testing, or annual fecal immunochemical testing (FIT), respectively, the models begin their simulation for US cohorts of individuals aged 66 to 90 years old in the year 2010 who have average risk of cancer and a specified comorbidity level (none, mild, moderate, or severe) and follow these individuals for their remaining lifetime. For reference, we also simulated cohorts aged 74 years and 76 years (75 years for colorectal cancer) with average health and corresponding average life expectancy. We assumed that comorbidity influenced non-cancer life expectancy but not cancer risk or progression, treatment, or cancer-specific survival.

Comorbidity-specific life tables—Non-cancer life expectancy was derived from comorbidity scores for 16 conditions derived from claims from a random 5% sample of non-cancer beneficiaries continuously enrolled with Medicare Parts A and B from 1992 to 2005 and residing in the Surveillance Epidemiology, and End Results (SEER) areas (20, 21, 22). Cox proportional hazard methods were used to estimate non-cancer age-conditional life tables for each gender and age combination using comorbidity as a covariate. Comorbidity was then grouped into four levels: none, mild, moderate, and severe, each with its own life

expectancy at a given age (Table 2). We used the weighted average of the comorbidity-specific life tables for the reference average-health cohorts. We extrapolated beyond the 13 years of available data by assuming that mortality rates converged abruptly to average US rates after that period. This is a conservative assumption for personalizing age of screening cessation because life expectancy is overestimated for those with moderate and severe comorbidity and is underestimated for those with no or mild comorbidities.

Analysis

For each cohort, we estimated the benefits and harms of screening at their current age. Diagnostic follow-up was based on current recommendations (breast and colorectal) or practice (prostate). Screening benefits were expressed as the life-years gained (LYG) and cancer deaths prevented (CDP) for every 1000 individuals screened at a given age. Harms were expressed as the false-positive tests and overdiagnosed cancers (i.e., cancer that would not have caused symptoms during an individual's lifetime) per 1000 individuals screened. The balance between harms and benefits was expressed as the number needed to screen to gain one life-year (NNS/LYG). For reference, we also determined, for each comorbidity level, the age at which the harms and benefits of screening (NNS/LYG) were similar to screening the average-health population at age 74.

Sensitivity Analysis

We varied our method for extrapolating comorbidity-specific life tables by assuming that the hazard ratio between the average-health life table and the comorbidity-specific life table at the 13th year of observation was maintained until death. For colorectal cancer, we also estimated the harms and benefits of colonoscopy screening by age and comorbidity level.

Role of the Funding Source

The funding sources had no role in study design and conduct; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, the National Cancer Institute, or the Centers for Disease Control and Prevention.

RESULTS

Screening Based on “Average” Comorbidity Level

At age 74, the average life expectancy for women across all comorbidity groups is 13.9 years. Screening 1000 women for breast cancer who have average health (and life expectancy) and who had been screened regularly prior to age 74 resulted in 79–96 false-positive tests (range across models) and 0.5–0.8 overdiagnosed cancers (Table 3). On the benefits side, 0.7–0.9 cancer deaths would be prevented and 5.8–7.6 life years gained (LYG), corresponding to 132–173 women that need to be screened at age 74 to gain one life-year.

Screening 1000 women age 76 and older for breast cancer yields increased harms and decreased benefits. Specifically, 146–198 women needed to be screened at age 76 to gain

one life-year. The balance of harms and benefits for prostate and colorectal cancer screening were mostly comparable except for the rates of overdiagnosis, which were orders of magnitude (15–100+ times, depending on the model) higher for prostate cancer vs. breast or colorectal cancer screening.

Screening by Comorbidity Level

In individuals with no comorbidities (i.e., individuals with longer-than-average life expectancy), screening 1000 regularly screened women aged 74 resulted in fewer overdiagnosed breast cancers (0.3–0.5) and more cancer deaths prevented (0.8–1.0) and LYG (6.6–8.5) compared to women the same age with average health. Consequently, the NNS/LYG of 117–150 was lower than that for the average-health population (Appendix Table 2). In fact, women with no comorbidities could be screened until age 76–78 and still yield a similar NNS/LYG as screening until age 74 in the average-health population (Figures 1 and 2). The same result is obtained for prostate and colorectal cancer screening (Figure 1, Appendix Table 2).

For the mild comorbidity group, screening for all three cancers at age 74 yielded similar harms and benefits as screening the average-health population (Figures 1 and 2, Appendix Table 2). In individuals with moderate comorbidity, screening at age 74 was considerably less favorable than in the average-health population at that age: overdiagnosed cancers were up to 15% higher, while cancer deaths prevented and LYG were up to 20% lower (Appendix Table 2). Screening those with moderate comorbidity at a median age of 72 (range 68–74) resulted in similar harms and benefits as screening the average-health population at age 74 (Figures 1 and 2, Appendix Table 2). Screening people with severe comorbidities for breast cancer at age 74 resulted in even more harms (1.3–1.9 overdiagnosed cancers) and fewer benefits (0.5–0.6 cancer deaths prevented; 3.5–4.5 LYG) (Appendix Table 2). In this group, screening at a median age of 66 (range 64–69) provided similar harms and benefits as screening the average-health population at age 74 (Figures 1 and 2, Appendix Table 2).

Sensitivity Analysis

If non-cancer mortality rates do not converge to average US rates after the 13 years of observed data, individuals with moderate and severe comorbidity could stop screening at even younger ages to have similar harms and benefits as screening the average-health population at age 74.

For colonoscopy, screening to age 70 for those with no, mild, or moderate comorbidity provided similar harms and benefits as screening the average-health population at age 70 (the last colonoscopy screening age for an individual regularly screened since age 50); among those with severe comorbidity the balance is comparable at age 60 (Appendix Table 4).

DISCUSSION

This is the first study to employ collaborative modeling to evaluate screening across three cancer sites. It systematically quantifies the balance of benefits and harms of screening older individuals for breast, prostate, and colorectal cancers by comorbidity level. The results are

robust across models and cancer sites and indicate that comorbidity affects screening benefits and harms and decisions about ages of screening cessation. These outcomes can directly inform individualized decisions about undergoing screening. Around 70% of the current US population aged 74 have none of the comorbidities noted in recent analyses to influence life expectancy (20). Our results suggest that this group could continue to be screened until age 76 and still have the same balance of benefits and harms expected from screening the average-health population until age 74. However, the 13% of the US population aged 65 to 74 with severe comorbidity should stop screening at age 66 to have the same balance of benefits and harms as seen among average-health groups undergoing screening from ages 50 to 74.

Our findings are consistent with and extend prior research addressing the upper age limits for cancer screening. For instance, Walter and Covinsky (7) found that screening for breast, cervical, and colorectal cancer until around age 60 for individuals in the lower quartile of population life expectancy has the same number needed to screen to prevent one cancer death as those with the median life expectancy at age 75. They also estimated that screening could be continued to age 85 for those in the upper quartile of life expectancy (7). This range is consistent with but wider than our model projections of 66 to 76 based on number needed to screen per life-year gained. When we use cancer deaths prevented rather than LYG, our ranges were closer to those of Walter and Covinsky, although our maximal upper age limit was still lower since we considered individuals without comorbidities (70% of the population) and they used the upper quartile (25%) of life expectancy.

A recent analysis looking at time lag to benefit after screening for breast and colorectal cancer suggests that screening for breast and colorectal cancer is most appropriate for patients with a life expectancy greater than 10 years (23). However, that study and others (6, 7, 24–29) provide little guidance on applying this framework in clinical practice, leaving it to clinical judgment to estimate life expectancy and individualize screening decisions. Several studies have investigated the relationship between comorbidity level and life expectancy (30–32) but do not address the question of how this relationship influences cancer screening. To date, only two analyses have directly related comorbidity level to cancer screening recommendations. One focused only on diabetes-related comorbidities and colorectal cancer screening (33) and one examined cardiovascular disease and breast screening (6). The current analysis is a multi-model collaborative analysis of three major cancers and includes a wider range of comorbidities than considered previously.

There is considerable debate about the value of PSA screening. The USPSTF recently concluded that PSA screening results in little or no reduction in prostate cancer-specific mortality while leading to substantial prostate cancer overdiagnosis. Based on these findings, the USPSTF recommends against routine prostate cancer screening. However, like other national guidelines panels (e.g., the ACS, the American Urological Association, the American College of Physicians), they recognized a role for screening in the context of appropriate patient-physician decision-making (34–37). Our modeling study provides clinicians with valuable information for such shared-decision making. Recent modelling studies indicate that overdiagnoses and unnecessary biopsies could be reduced by stopping prostate cancer screening at age 69, raising the PSA threshold for biopsy referral for men

above this age, or restricting further screening to men with low comorbidity (17, 18). Our results confirm these results and underscore that overdiagnosed cancers detected via PSA screening are orders of magnitude higher than for breast or colorectal cancer screening. If personalized PSA screening strategies achieve a sufficiently favorable balance of outcomes, our results advocate tailoring of screening cessation according to comorbidity-based life expectancy.

Our results provide clinicians with data for use in informed decision-making discussions about who might consider continuing screening and for how long. For example, if a clinician is meeting with a regularly-screened 70-year old patient with COPD, our results indicate that this individual falls in the severe comorbidity level and, depending on patient preferences, the benefits of screening may no longer outweigh the potential harms. However, a 76-year old individual with no comorbidities might consider attending another screen. The final decision about screening should depend on individual patient preferences. Prevention of death from cancer is one outcome to consider, but some patients may be more concerned with impact on other outcomes such as quality of life or functional independence. Individuals may also prefer to be detected at earlier stages when less intensive treatment may be needed, compared to somewhat later diagnosis and more aggressive therapy, even if survival is unchanged. In such a situation, a healthy patient may choose to continue (for example) breast cancer screening up to age 80, where the mortality benefit is small, but early detection can find the cancer early when less aggressive treatment is required.

The fact that comorbidity-specific conclusions about age-specific benefits and harms differ meaningfully from those included in clinical guidelines highlights the tension between the need to provide public health recommendations for the general population and the potential advantages of using a more personalized approach. Our suggested approach of continuing screening in the healthy and earlier cessation in the sickest individuals does not increase the number of screens required in the population but rather leads to a more efficient allocation of resources, increasing the benefit and decreasing the harms to the growing older population (38). The age-, gender-, and comorbidity-specific life expectancies used for these analyses also provide clinicians and the general screening-eligible population with a foundation for discussing preferences for benefits and harms, facilitating individual decision-making.

The testing intervals for colorectal and breast cancer were chosen according to the latest USPSTF guidelines, but our conclusions can be generalized to other intervals. The screening cessation ages are determined in relation to screening the average-health population up to age 74. When choosing a different screening interval, such as annual mammography for breast cancer, the benefits and harms will be different for screening the average-health population at age 74. The benefits and harms by comorbidity level will change accordingly, such that the optimal screening cessation age by comorbidity remains the same.

Despite the innovation and strengths of our approach, there are several caveats that should be considered in evaluating our results. First, we chose the balance of harms and benefits as our primary metric. We did not explicitly consider complications from screening and diagnostic follow-up as harms, but these would be proportional to the number of (false-

positive) screening tests. Costs per quality-adjusted life-year gained are another common metric used in many countries, but this is not widely accepted in the US (39–43). Second, we assumed that comorbidity level only influenced life expectancy and not cancer risk or biology. Health conditions such as diabetes are known to be associated with obesity and other lifestyle factors (44) which, in turn, can be associated with improved mammography performance (45) and elevated breast (46–48) or reduced prostate (49) cancer risk. Conversely, adverse events of screening, such as perforations with colonoscopy, are also associated with comorbidities (50). In the future, it will be important to extend our work to capture the known impact of specific comorbidities on other model parameters. For now, competing non-cancer mortality is the single most germane parameter in screening decisions for the oldest age groups so that our conclusions should be robust (27). Third, we only estimated harms and benefits of screening by comorbidity for people aged 66 years and older because life expectancy estimates by comorbidity were obtained from SEER-Medicare data.

Next, we only considered individuals regularly screened since age 50 to demonstrate how current screening recommendations could be adapted based on comorbidity level. In general, stopping ages are higher in individuals who are unscreened or have skipped previous screening rounds because they have a higher risk of prevalent cancer. Furthermore, the models used life tables based on non-cancer cases and, therefore, do not include cancer-specific mortality for cancers other than the one targeted by screening. This underestimates the true rate of competing other-cause mortality, and therefore the harm-benefit ratios, but does not affect our internal comparisons of comorbidity level groups to the average-health population. Finally, we did not consider situations in which the comorbidity level decreased (e.g., from severe to moderate level) after the age of screening cessation. Given the chronic nature of the comorbid conditions in older ages, this is a reasonable assumption.

Overall, the results across models and cancer sites were very robust and strongly suggest that the age of screening cessation based on comorbidity levels varies by nearly a 10-year interval around the age cut-point of 74 included in current breast and colorectal cancer screening recommendations. Our data on common chronic health conditions and their associated comorbidity level, together with model projections of screening benefits and harms at each of these comorbidity levels, can inform discussions between providers and their older patients about personalizing decisions about when to stop cancer screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge Drs. Hyunsoon Cho, Carrie Klabunde, and Robin Yabroff from the National Cancer Institute for their permission to use the comorbidity-specific life tables.

Funding

This work was supported by the National Cancer Institute at the National Institutes of Health and the Centers for Disease Control and Prevention (grant Numbers U01CA097426, U01CA115953, U01CA152959, U01CA157224, U01CA088283, U01CA152958); supported in part by the National Cancer Institute at the National Institutes of

Health (grant numbers KO5CA96940 to JSM and P01CA154292 to JSM, CBS, NTvR, EAH, HJdK); the Dutch Cancer Society (grant numbers 94-869, 98-1657, 2002-277 and 2006-3518 to EAH, HJdK); and the Netherlands Organisation for Health Research and Development (grant numbers 002822820, 22000106, 50-50110-98-311 to EAH, HJdK). Breast Cancer Surveillance Consortium data collection and sharing used in some parameters for modeling breast cancer screening was supported by the National Cancer Institute at the National Institutes of Health (grant numbers U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040, and HHSN261201100031C). The funding sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, the National Cancer Institute, or the Centers for Disease Control and Prevention.

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Figure 1.

Number needed to screen per life-year gained (NNS/LYG) for screening at the plotted age by comorbidity level. The horizontal dashed line represents the NNS/LYG for screening the average-health population until age 76 (75 for colorectal cancer). The vertical dashed lines indicate the age for each comorbidity group at which screening provided similar harms and benefits as screening at age 74 in the average-health population (oldest age for which the NNS/LYG falls under the vertical dotted line). Panels show number needed to screen to gain 1 life-year (NNS/LYG) projected by MISCAN-Fadia and Model G-E model for breast cancer; by MISCAN-Prostate and FHCRC model for prostate cancer; and by MISCAN-Colon, CRC-SPIN, and SimCRC for colorectal cancer.

Figure 2.

Age at which harms and benefits of screening were similar to that for individuals with average health undergoing screening at age 74. The grey bars represent the median age while the uncertainty bars represent the range across all models and cancer sites. For no comorbidity, the lowest cessation age across models and cancer sites coincides with the median age (see Figure 1 and Appendix Table 2).

Selected clinical model outputs for 74-year old individuals who have average health (and life expectancy) and who had been screened regularly prior to age 74, in the presence and absence of screening at age 74.

Table 1

	Breast Cancer		Prostate Cancer		Colorectal Cancer		
	MISCAN-Fadia	G-E model	MISCAN-Prostate	FHCRC Prostate	MISCAN-Colon	CRC-SPIN	SimCRC
Lifetime probability of developing cancer without screening at age 74	6.9%	8.2%	7.9%	4.7%	1.9%	1.3%	1.1%
Lifetime probability of developing cancer with screening at age 74	7.2%	8.4%	9.8%	6.1%	1.8%	1.2%	1.0%
Prevalence of undiagnosed cancer immediately before a screening at age 74	9.3% *	1.14%	4.4%	13.3%	0.19%	0.06%	0.09%
Prevalence of undiagnosed cancer immediately after a screening at age 74	8.2% *	0.09%	1.0%	11.3%	0.06%	0.02%	0.05%

* The large difference in undiagnosed cancers between the models reflect differences in modeling approach. MISCAN-Fadia includes cancers from a very small tumor size (0.1 mm) not yet detectable by mammography.

MISCAN: Microsimulation Screening Analysis; Fadia: Fatal diameter; G-E: Georgetown-Einstein; FHCRC: Fred Hutchinson Cancer Research Center; CRC-SPIN: ColoRectal Cancer Simulated Population model for Incidence and Natural history; SimCRC: Simulating ColoRectal Cancer

Table 2

Overview of comorbidity levels, associated conditions, and life expectancies at ages 68, 74 and 78 years

Comorbidity group	Percent of population at age 74	Conditions included*	HR [†]	Life expectancy at age 68, y		Life expectancy at age 74, y		Life expectancy at age 78, y	
				Men	Women	Men	Women	Men	Women
No comorbidity	69%	None	1	16.6	19.3	13.1	15.1	10.7	12.4
Mild comorbidity	2%	History of MI, acute MI, ulcer or rheumatologic disease	1.01–1.38	15.4	17.1	12.5	13.1	9.8	10.9
Moderate comorbidity	12%	(Cardio-)vascular disease; paralysis; diabetes; or combinations of diabetes with MI, ulcer, or rheumatologic disease	1.39–1.66	14.4	16.3	11.0	12.4	8.6	9.9
Severe comorbidity	17%	AIDS; COPD; mild or severe liver disease; chronic renal failure; dementia; congestive heart failure; or combinations of aforementioned diseases not categorized under moderate comorbidity	1.67	10.8	13.3	8.1	9.8	6.4	7.7
Average health population	100%	All		15.7	18.3	11.9	13.9	9.6	11.2

HR: Hazard ratio; y year; MI myocardial infarction; AIDS Acquired Immune Deficiency Syndrome; COPD chronic obstructive pulmonary disease

* Any one of the conditions listed places an individual in the associated comorbidity level in the first column of the table and its life expectancy at age 68, 74 or 78. Conditions included are those that affect life expectancy. See Appendix Table 2 for life expectancies at other ages. See Appendix Table 3 for ICD-09 codes for the conditions.

[†] Hazard ratio for all-cause mortality compared to no comorbidity for the conditions included in each comorbidity level

Table 3

Benefits and harms of screening 1,000 regularly screened individuals at age 74 or 76 (75 years for colorectal cancer) with average health, by cancer site and model

Cancer site / model / age of screening	Harms*		Incremental benefits*		Balance	
	False-positive tests	Over-diagnosed cancers	Life-years gained [†]	Cancer deaths prevented	NNS/LYG	NNS/CDP
Breast cancer						
<i>MISCAN-Fadia</i>						
74 years	79	0.8	7.6	0.9	132	1125
76 years	77	1.0	6.9	0.9	146	1102
<i>G-E model</i>						
74 years	96	0.5	5.8	0.7	173	1421
76 years	96	0.6	5.1	0.7	198	1474
Prostate cancer						
<i>MISCAN-prostate</i>						
74 years	116	19.7	6.6	1.2	150	830
76 years	136	24.5	6.3	1.2	159	820
<i>FHCRC prostate cancer model</i>						
74 years	242	14.5	6.1	0.8	165	1263
76 years	268	16.2	5.1	0.7	197	1371
Colorectal cancer						
<i>MISCAN-Colon</i>						
74 years	39	0.3	6.2	0.9	161	1118
75 years	39	0.4	5.5	0.8	182	1218
<i>CRC-SPIN</i>						
74 years	37	0.0	4.4	0.6	229	1618
75 years	37	0.0	3.7	0.6	272	1685
<i>SimCRC</i>						
74 years	38	0.1	4.9	0.8	227	1411
75 years	38	0.1	4.3	0.7	258	1522

* Results are per 1,000 individuals screened according to guidelines (breast and colorectal) or current practice (prostate) since age 50

[†]One life-year gained per 1,000 individuals corresponds with 0.4 days gained per individual.

NNS/LYG: Number needed to screen to gain 1 life-year; NNS/CDP: Number needed to screen to prevent 1 cancer death; MISCAN: Microsimulation Screening Analysis; Fadia: Fatal diameter; G-E: Georgetown-Einstein; FHCRC: Fred Hutchinson Cancer Research Center; CRC-SPIN: ColoRectal Cancer Simulated Population model for Incidence and Natural history; SimCRC: Simulating ColoRectal Cancer