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Identifying Populations at Elevated Risk of Cancer Outside Those Traditionally Targeted for Screening and Prevention

Annual Meeting of the American Association for Cancer Research.
April 8 – 13, 2022.
New Orleans, Louisiana

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INTRODUCTION

- Currently, populations are identified for cancer screening interventions one cancer type at a time, through consideration of age, sex, and in the case of lung cancer, smoking history.
  - In the United States, screening is recommended for breast, cervix, and colorectal cancers in the general population, and for lung cancers defined by detailed smoking history requirements.[1] Prostate cancer screening for males aged 55 to 69 years is considered an individual decision and is grade C, whereas the other recommended screening is grade A/B by the United States Preventive Services Task Force.[2]
- New technological developments in cancer screening, such as multi-cancer early detection (MCED) tests[3-5] can detect signals from multiple cancer types from a single blood draw. Therefore, it is important and timely to understand the overall cancer burden in populations currently targeted for single-cancer screenings, as well as those currently outside those recommendations, such as persons aged 40–49 years.
  - In particular, understanding the spectrum of absolute risk is needed to contemplate cancer screening strategies for both the general population and high-risk populations.
- Large prospective cohort studies that collect detailed lifestyle and environmental risk factors offer unique opportunities to understand variability in age-specific absolute risk of any invasive cancer.

OBJECTIVES

- We used the American Cancer Society's long-term prospective cohort studies to:
  - Identify the common, independent risk factors for developing any invasive cancer and
  - Calculate associated 5-year absolute risks for cohort subgroups of interest defined by risk factors identified in the first objective

METHODS

Cohort Description

- In this analysis, we examined a broad range of cancer risk factors using two large prospective American Cancer Society cohorts, the Cancer Prevention Study-II Nutrition Cohort (CPS-IINC) enrolled from 1992-1993 and Cancer Prevention Study 3 (CPS-3) enrolled from 2006-2013.[6,7] Brief summary of inclusion criteria for each study are outlined below:
  - **CPS-IINC:** Participants in the earlier CPS-II Mortality Cohort[6] who resided in one of 21 U.S. states with population-based cancer registries that ascertained at least 90% of incident cancers by 1990, and completed a 10-page self-administered survey (questions on demographic, lifestyle, medical, and behavioral factors). Most CPS-IINC participant were aged 50–74 years at enrollment in 1992/1993.
  - **CPS-3:** aged 30–65 years, no prior personal history of cancer, completed a brief enrollment survey, and provided a blood sample at enrollment. Enrollment was across 35 U.S. states, the District of Columbia, and Puerto Rico at various community events between 2006 and 2013.
- In this analysis, we excluded participants from CPS-IINC and CPS-3 for the following reasons:
  - Lost to follow-up (n=6,192)
  - Reported, but unverified cancer or missing diagnosis date (n=952)
  - Missing sex or age (n=133)
  - Revoked or duplicate record (n=209)
  - Died before their survey return date (n=7), or
  - CPS-3 participants who lived in a state where cancer registry linkages had yet to be completed (n=24,287).
- We also excluded participants who self-reported a history of cancer prior to enrollment (n=26,094) because of the lack of detail on cancer type or time since diagnosis, and because risk factors associated with second cancers differ from first cancers.

Outcomes and Covariates

- Candidate risk factors were identified based on those reported for single cancer types by the Washington University Your Disease Risk™ resource (https://publichealthsciences.wustl.edu/community-focus/your-disease-risk-assessment-tool/).[8]
- All risk factors were self-reported at time of enrollment and only those queried in both cohorts were included (**Table 1**).
  - In women only the following potential risk factors were also examined: parity, hysterectomy, tubal ligation, ≥5 years of oral contraceptive use, and exogenous postmenopausal hormone use.
- Cancer ascertainment:
  - CPS-IINC cancers were self-reported on the 1997 follow-up survey (~5 years after baseline) and verified through medical records or routine linkage with state cancer registries.
  - All CPS-3 participants were linked routinely with state cancer registries to identify all reportable cancer diagnoses through December 31, 2015.

Table 1. Potential risk factors examined in both cohort studies via baseline self-reported questionnaire

Potential Risk Factor	Categorizations used in present study[a]
Age	Single year
Sex	Male/female
Race	Non-Hispanic white, non-Hispanic Black, other/ mixed race
First Degree Family History of Cancer	Yes, no
Body Mass Index	<18.5 kg/m², 18.5–<25.0, 25–<27.5, 27.5–<30.0, 30–<35.0, ≥35
Current Alcohol Use	none, <1 drink/day, 1–2 drinks/day, >2 drinks/day
Smoking History	never, former (<10, 10–<20, 20–<30, and ≥30 years since quitting), current
Moderate-to-Vigorous Physical Activity	0, >0–<7.5, 7.5–<15.0, ≥15.0 metabolic equivalents-hours per week
≥5 Daily Servings of Fruits or Vegetables	Yes, no
Limiting Red Meat Consumption	Yes, no
History of Hypertension	Yes, no
Daily Multivitamin Use	Yes, no

[a]Missing category was added for each potential risk factor.

Statistical Analysis

- Multivariable Cox proportional hazards models were used to estimate relative risks (RR) and 95% confidence intervals (CIs) for associations between potential risk factors and subsequent overall risk of any invasive cancer.
  - Only statistically significant ($P<0.05$) variables were retained in final multivariable-adjusted models.
- The Individualized Coherent Absolute Risk Estimation tool packaged in R used these RRs to estimate absolute risk for 5-year age groups expressed as percent risk of any cancer in 5 years.[9]
  - A cut point of 2% absolute risk per 5 years was used based on SEER data showing this is consistent with the absolute risk of any cancer at age 50 years, when most established screenings begin.[10]
  - We re-ran models for men and women including only the three risk factors with the largest RR from the multivariable-adjusted Cox models so as to provide parsimonious absolute risk models.

KEY RESULTS: AMONG PERSONS UNDER AGE 50 YEARS, SMOKING STATUS WAS THE MOST IMPORTANT FACTOR DIFFERENTIATING RISK

- Several risk factors including smoking history, obesity, alcohol, family history of cancer, and various chronic medical conditions (e.g., diabetes, hypertension) were independently associated with a higher risk of cancer.
- Persons above age 50 years, regardless of other risk factors considered, had at least 2% absolute risk per 5 years.
- Increasing age and smoking were the two risk factors most strongly associated with 5-year risk of developing any cancer.
- For men under age 50, absolute risk of any cancer did not exceed 2% except for men ages 45–49 years who currently smoke with BMI>30 and a family history of cancer (**Figure 1A**).
- For women under age 50, absolute risk exceeded 2% starting at age 40–44 years for current or recent former smokers with high BMI, and women who were non-smokers at age 50+ years had over 2% absolute risk (**Figure 1B**).

Absolute Risk of of Developing Any Invasive Cancer in Males and Females by Risk Factor Profile

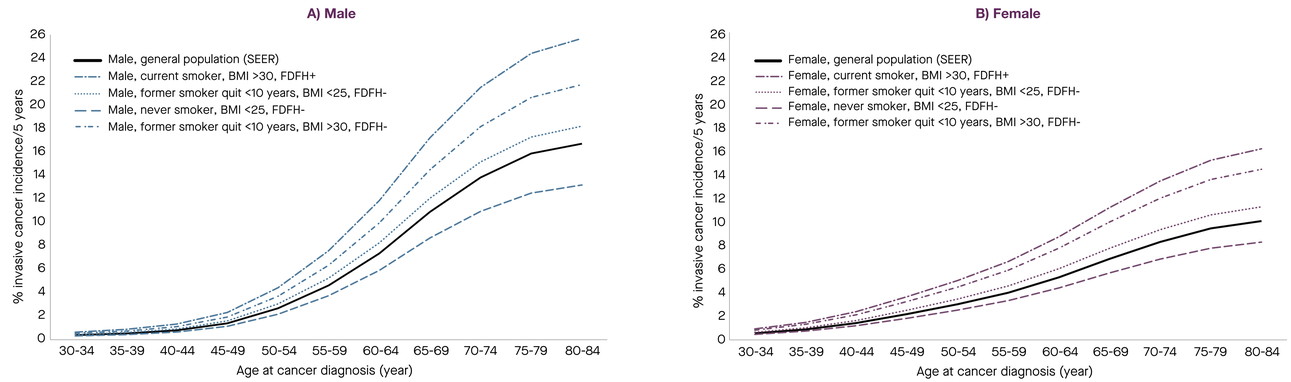

Figure 1. Age-specific incidence curves describing absolute risk for highest risk groups from parsimonious absolute risk models (current smoker, BMI >30, first degree family history of cancer) and lowest risk groups (never smoker, BMI 25-30, no first degree family history of cancer) compared to general population (SEER), American Cancer Society Cancer Prevention Studies II and 3. A) Males and B) Females. Abbreviations: BMI, body mass index; FDFH, first degree family history of cancer; SEER, Surveillance, Epidemiology, and End Results Program.

SUPPORTING DATA

- A total of 429,991 participants were included (CPS-IINC: 81,280 women and 73,056 men, CPS-3: 211,377 women, and 64,278 men).
- CPS-IINC participants were older, enrolled about 20 years earlier and, accordingly, had different distributions of certain risk factors (**Table 2**).

Table 2. Distribution of demographic and cancer risk factor baseline characteristics by cohort and participant sex, American Cancer Society Cancer Prevention Study cohorts, 1992–2013

Variable	CPS-II (N=153,336)		CPS-3 (N=275,655)	
	Male N=73,056	Female N=81,280	Male N=64,278	Female N=211,377
Follow-up time, years, mean (SD)	4.7 (0.99)	4.8 (0.7)	3.6 (1.17)	3.5 (1.14)
Baseline year, median (range)	1992 (1992–1993)	1992 (1992–1993)	2012 (2006–2015)	2012 (2006–2015)
Age at start of follow-up, median (range)	64 (41–93)	62 (40–90)	48 (20–82)	48 (19–80)
Diagnosed with at least one invasive cancer within 5 years				
No	66,467 (91)	77,295 (95.1)	63,137 (98.2)	207,866 (98.3)
Breast, prostate, colorectal or cervical cancer	3,826 (5.2)	2,004 (2.5)	546 (0.8)	1,714 (0.8)
All other cancers	2,763 (3.8)	1,981 (2.4)	595 (0.9)	1,797 (0.9)
Race				
White	71,145 (97.4)	79,047 (97.3)	53,066 (82.6)	176,090 (83.3)
Black	902 (1.2)	1,256 (1.5)	2,557 (4)	10,090 (4.8)
Other	1,009 (1.4)	977 (1.2)	8,655 (13.5)	25,197 (11.9)
First-degree family history of cancer				
No	44,265 (60.6)	47,015 (57.8)	22,193 (34.5)	75,566 (35.7)
Yes	28,791 (39.4)	34,265 (42.2)	27,561 (42.9)	100,895 (47.7)
Missing	0 (0)	0 (0)	14,524 (22.6)	34,916 (16.5)
Body mass index kg/m²				
18.5 – < 25	25,578 (35)	40,739 (50.1)	15,022 (23.4)	82,497 (39)
25 – < 27.5	22,729 (31.1)	16,518 (20.3)	15,870 (24.7)	35,663 (16.9)
27.5 – < 30	12,951 (17.7)	8,715 (10.7)	12,419 (19.3)	24,365 (11.5)
30 – < 35	8,601 (11.8)	8,905 (11)	13,499 (21)	34,919 (16.5)
35+	1,779 (2.4)	3,613 (4.4)	6,733 (10.5)	30,114 (14.2)
Other/Missing	1,418 (1.9)	2,790 (3.4)	735 (1.1)	3,819 (1.8)

Variable	CPS-II (N=153,336)		CPS-3 (N=275,655)	
	Male N=73,056	Female N=81,280	Male N=64,278	Female N=211,377
Current alcohol use, drinks per day				
None	23,892 (32.7)	36,935 (45.4)	12,161 (18.9)	45,250 (21.4)
<1/Day	28,054 (38.4)	30,860 (38)	39,147 (60.9)	138,339 (65.4)
1-2/Day	9,138 (12.5)	6,156 (7.6)	6,826 (10.6)	13,205 (6.2)
>2/Day	8,949 (12.2)	3,809 (4.7)	2,781 (4.3)	2,540 (1.2)
Missing	3,023 (4.1)	3,520 (4.3)	3,363 (5.2)	12,043 (5.7)
Smoking history				
Never smoker	23,481 (32.1)	44,256 (54.4)	41,973 (65.3)	144,337 (68.3)
30+ years since quitting	11,623 (15.9)	6,831 (8.4)	3,366 (5.2)	8,927 (4.2)
20–<30 years since quitting	12,225 (16.7)	7,979 (9.8)	3,641 (5.7)	13,030 (6.2)
10–<20 years since quitting	9,744 (13.3)	6,744 (8.3)	4,434 (6.9)	14,249 (6.7)
<10 years since quitting	8,614 (11.8)	7,242 (8.9)	5,385 (8.4)	16,070 (7.6)
Current smoker	6,687 (9.2)	6,888 (8.5)	4,246 (6.6)	12,114 (5.7)
Missing	682 (0.9)	1,340 (1.6)	1,233 (1.9)	2,650 (1.3)
Physical Activity (METS)				
None/Sedentary	8,871 (12.1)	7,457 (9.2)	2,421 (3.8)	9,418 (4.5)
>0–<7.5	21,536 (29.5)	27,413 (33.7)	8,050 (12.5)	38,720 (18.3)
7.5–<15	19,097 (26.1)	23,943 (29.5)	6,829 (10.6)	26,443 (12.5)
15+	22,435 (30.7)	21,216 (26.1)	29,490 (45.9)	86,932 (41.1)
Missing[a]	1,117 (1.5)	1,251 (1.5)	17,488 (27.2)	49,864 (23.6)

SD= standard deviation, METs= metabolic energy equivalents
[a]Participants who did not complete the more detailed survey in CPS-3 have missing data

CONCLUSIONS

- These results fill an important gap in the literature by prioritizing the most important risk factors for developing any cancer in five years and then quantifying absolute risks for population subgroups (i.e., male, current smokers, BMI >30, and family history of cancer), to identify those who may benefit most from expanded cancer screening and prevention.
- Smoking history is important in differentiating absolute risk of any cancer in most adults, including those under age 50 years.
- More research to understand the extent to which other cancer risk factors influence risk for specific populations aged <50 years should be carried out. This is particularly important now that average 45–49 year olds are being included in colorectal cancer screening guidelines.

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Disclosures

Study funded by GRAIL, LLC, a subsidiary of Illumina, Inc. All financial relationships disclosed at abstract submission.

Acknowledgements

The authors express sincere appreciation to all Cancer Prevention Study-II and Cancer Prevention Study-3 participants, and to each member of the study and biospecimen management group. The authors would like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries and cancer registries supported by the National Cancer Institute's Surveillance Epidemiology and End Results Program.

Funded by GRAIL, LLC, a subsidiary of Illumina, Inc. Writing and editorial assistance provided by DeFino Consulting, LLC (Chicago, IL).