

Original Investigation

Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States

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IMPORTANCE Lifestyle factors are important for cancer development. However, a recent study has been interpreted to suggest that random mutations during stem cell divisions are the major contributor to human cancer.

OBJECTIVE To estimate the proportion of cases and deaths of carcinoma (all cancers except skin, brain, lymphatic, hematologic, and nonfatal prostate malignancies) among whites in the United States that can be potentially prevented by lifestyle modification.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study analyzes cancer and lifestyle data from the Nurses' Health Study, the Health Professionals Follow-up Study, and US national cancer statistics to evaluate associations between lifestyle and cancer incidence and mortality.

EXPOSURES A *healthy lifestyle pattern* was defined as never or past smoking (pack-years <5), no or moderate alcohol drinking (≤ 1 drink/d for women, ≤ 2 drinks/d for men), BMI of at least 18.5 but lower than 27.5, and weekly aerobic physical activity of at least 75 vigorous-intensity or 150 moderate-intensity minutes. Participants meeting all 4 of these criteria made up the low-risk group; all others, the high-risk group.

MAIN OUTCOMES AND MEASURES We calculated the population-attributable risk (PAR) by comparing incidence and mortality of total and major individual carcinomas between the low- and high-risk groups. We further assessed the PAR at the national scale by comparing the low-risk group with the US population.

RESULTS A total of 89 571 women and 46 339 men from 2 cohorts were included in the study: 16 531 women and 11 731 men had a healthy lifestyle pattern (low-risk group), and the remaining 73 040 women and 34 608 men made up the high-risk group. Within the 2 cohorts, the PARs for incidence and mortality of total carcinoma were 25% and 48% in women, and 33% and 44% in men, respectively. For individual cancers, the respective PARs in women and men were 82% and 78% for lung, 29% and 20% for colon and rectum, 30% and 29% for pancreas, and 36% and 44% for bladder. Similar estimates were obtained for mortality. The PARs were 4% and 12% for breast cancer incidence and mortality, and 21% for fatal prostate cancer. Substantially higher PARs were obtained when the low-risk group was compared with the US population. For example, the PARs in women and men were 41% and 63% for incidence of total carcinoma, and 60% and 59% for colorectal cancer, respectively.

CONCLUSIONS AND RELEVANCE A substantial cancer burden may be prevented through lifestyle modification. Primary prevention should remain a priority for cancer control.

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Cancer is the second leading cause of death in the United States, with 1.6 million new cancer cases and 0.6 million cancer deaths projected to occur in 2016.¹ The cancer mortality rate, age-standardized to the 2000 US standard population, decreased from 199 to 163 per 100 000 between 1969 and 2013.² However, this decline (17.9%) has been modest compared with the dramatic decrease in heart disease mortality (67.5%) during the same period, highlighting the need for further efforts in cancer prevention and treatment.

Epidemiologic studies have established several lifestyle factors that increase cancer risk, such as smoking, alcohol use, obesity, and physical inactivity.³ However, this substantial body of knowledge has been challenged by a recent study,⁴ which found a high correlation between the number of stem cell divisions of a given tissue and the lifetime risk of cancer in that tissue. This finding led some to conclude that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions, while most is due to random mutations arising during stem cell divisions, so-called bad luck. This study has been widely covered by the press and has created confusion for the public regarding the preventability of cancer. Many arguments against the bad luck hypothesis have been made,⁵⁻¹² including the notion that external environmental factors may influence cancer development through promotion of DNA damage¹³; yet none of these reports has provided original data to assess the preventability of cancer through modification of extrinsic factors.

Therefore, we estimated the contributions of common lifestyle factors to cancer burden by comparing cancer incidence and mortality between the participants who had a healthy lifestyle (low-risk group) and those who did not (high-risk group) in 2 nationwide cohorts. We further explored the potential capability of lifestyle modification for cancer prevention at the national scale by comparing the low-risk subgroup of our cohorts with the US population. Because our cohorts' participants were predominantly whites, to avoid any influence of different racial distributions on the comparison with the general population, we only included whites in the analysis.

Methods

Study Population

The Nurses' Health Study (NHS)¹⁴ and Health Professionals Follow-up Study (HPFS)¹⁵ are 2 ongoing US cohorts that respectively enrolled 121 700 registered female nurses aged 30 to 55 years with about 70% response rate in 1976 and 51 529 male health professionals aged 40 to 75 years with about 25% response rate in 1986. Similar follow-up procedures have been used in the 2 cohorts.^{14,16} In brief, participants completed a detailed questionnaire about their medical history and lifestyle at baseline and every 2 years thereafter. Dietary intake was assessed using validated food frequency questionnaires every 4 years. The response rates have been 95.4% in the NHS and 95.9% in the HPFS for each of the questionnaires through 2010. In the present study, we used as baseline 1980 for the NHS and 1986 for the HPFS, when we first collected detailed lifestyle data.

Key Points

Question How many cancer cases and deaths in the United States can be attributed to lifestyle factors?

Findings In this cohort study of a portion of the US white population, about 20% to 40% of cancer cases and about half of cancer deaths can be potentially prevented through lifestyle modification. These figures increased to 40% to 70% when assessed with regard to the population of US whites, and the observations are potentially applicable to broader segments of the US population.

Meaning Primary prevention should remain a priority for cancer control.

We identified 16 531 women from the NHS and 11 731 men from the HPFS who met the 4 healthy lifestyle criteria for the low-risk group: (1) never smoking or past smoking (pack-years <5); (2) no or moderate alcohol drinking (≤ 1 drink/d for women, ≤ 2 drinks/d for men), as recommended by the Dietary Guidelines for Americans¹⁷; (3) BMI of at least 18.5 and lower than 27.5; and (4) weekly aerobic physical activity of at least 75 vigorous-intensity or 150 moderate-intensity minutes (7.5 metabolic-equivalent [METs] hours per week), as recommended by the 2008 Physical Activity Guidelines for Americans.^{18,19} The remaining 73 040 women and 34 608 men who did not meet all the 4 criteria and had complete lifestyle data were classified into the high-risk group (eFigure 1 in the Supplement). This study was approved by the institutional review board at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health. Written informed consent was obtained from all study participants.

Lifestyle Assessment

Height, body weight, smoking, and physical activity were self-reported on biennial questionnaires. Physical activity was calculated by summing the products of time spent on a variety of leisure-time activities with the average MET for that activity.²⁰ Alcohol use was self-reported every 4 years on the food frequency questionnaires.²¹ We calculated the overall dietary score according to the Alternate Healthy Eating Index,²² which is designed to target food choices and macronutrient sources associated with reduced chronic disease risk. Detailed sources of US lifestyle data are provided in the eMethods in the Supplement.

Outcome Ascertainment

The primary outcomes of this study were incidence and mortality of total and major individual carcinomas. For total carcinoma, we excluded from all cancers those in the skin, brain, lymphatic, and hematopoietic tissues because these cancers likely have other strong environmental causes than the ones considered in the current study, such as UV exposure, infections, irradiation, and exposures to carcinogenic substances. The total carcinomas we studied account for about 90% of all cancer deaths among the US white population. For individual carcinomas, we included those with at least 10 cases occurring in our low-risk subpopulation. Given the concern about

Table 1. Comparison of Lifestyle Factors in the Low- and High-Risk Groups and in the US White Population in 2010^a

Variable	Women			Men		
	Low-Risk Group	High-Risk Group	US White Population	Low-Risk Group	High-Risk Group	US White Population
Smoking, % ^b						
Never	78	31	66	83	26	54
Past	22	61	18	17	69	25
Current	0	8	16	0	5	21
Met 2008 federal physical activity guidelines, % ^{b,c}	100	63	47	100	83	54
BMI, mean	23.4	26.7	26.9	24.4	27.3	26.4
Alcohol consumption, median, drinks/d	0.1	0.1	0.5	0.4	0.7	1.4
AHEI score, mean	48.1	46.4	39.0	43.8	40.5	35.7

Abbreviations: AHEI, Alternative Healthy Eating Index²²; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a All variables are age-adjusted based on the age distribution of the US population in 2000.

^b Smoking and physical activity data in the United States were derived from the National Health Interview Survey, 2012 (eMethods in the Supplement). Past

smokers were persons who had smoked at least 100 cigarettes in their lifetime but no longer smoked at all.

^c The 2008 federal guidelines^{18,19} recommend that for substantial health benefits, adults should perform at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity or an equivalent combination.

overdiagnosis for indolent prostate cancer by prostate-specific antigen (PSA) screening,²³ we included only fatal prostate cancer in our analysis. The number of cases for each cancer is provided in eTable 1 in the Supplement.

In both cohorts, self-reported diagnoses of cancer were obtained on biennial questionnaires, and participants who reported a cancer diagnosis were asked for permission to acquire their medical records and pathologic reports. Study physicians, blinded to exposure information, reviewed medical records to confirm cancer diagnosis. Most of the deaths were identified through family members or the postal system in response to the follow-up questionnaires. We also searched the names of persistent nonresponders in the National Death Index. More than 96% of deaths have been identified using these methods.²⁴ The cause of death was assigned by study physicians blinded to exposure data.

National Incidence and Mortality Data

We obtained the US cancer incidence²⁵ and mortality²⁶ data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. To parallel the age distribution and follow-up time of our cohorts, we selected data collected from participants 40 years or older, and from 1976 through 2012 for women and from 1986 through 2012 for men. For cancer mortality, the follow-up data were available up to 2011. We included only white participants, as we did in our cohort population. All incidence and death rates were age-standardized to the 2000 US standard population using the National Cancer Institute's SEER*Stat software (version 8.1.5).²⁷

Statistical Analysis

In our cohorts, we calculated person-years of follow-up for each participant from the age at the date of returning the baseline questionnaire until the age at the date of death, loss to follow-up, or end of follow-up (June 1, 2012, for the NHS; January 31, 2012, for the HPFS), whichever came first. For cancer incidence analysis, follow-up was also censored when a partici-

pant was diagnosed with any of the cancers under study. Age- and sex-specific rates were calculated for each of the 10 age groups (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and ≥85 years) and then standardized to the 2000 US standard population.

Our primary outcome measure was the population-attributable risk (PAR, %), which included 2 sets: one was based on comparison within our cohorts and calculated as the difference in the cancer rates between the low- and high-risk groups divided by the rate in the high-risk group; and the other one was estimated by comparing the cancer incidence and mortality in our low-risk group with the national SEER rates. The PAR can be interpreted as the proportion of cases that would not occur if all individuals adopted the lifestyle of the low-risk population. Details about derivation of the 95% confidence intervals (CIs) for PAR are provided in the eMethods in the Supplement.

Results

Table 1 lists the comparison of major lifestyle factors in low- and high-risk groups of our cohorts and the broader white US population. Although diet was not a specific criterion, our low-risk group had a higher Alternate Healthy Eating Index score than our high-risk group. The lifestyle profile in the white US population was generally even worse than that in our high-risk group.

Table 2 lists the age-standardized incidence and mortality rates and the corresponding PAR estimates for total carcinomas among the 2 risk groups of our cohorts and the whites in the US population. The incidence rates of total carcinoma per 100 000 population in the low- vs high-risk groups were 463 vs 618 in women, and 283 vs 425 in men, giving rise to a PAR of 25% (95% CI, 21%-29%) in women and 33% (95% CI, 28%-38%) in men. A higher PAR was observed for mortality (48% [95% CI, 44%-53%] in women and 44% [95% CI, 39%-48%] in men). When further com-

Table 2. Incidence and Mortality Rates of Total Carcinomas in the Low- and High-Risk Groups and in the General US White Population, and the Corresponding Estimates of Population Attributable Risk^a

Variable	Participants, No. per 100 000			PAR, % (95% CI)	
	Low-Risk Group	High-Risk Group	US White Population ^b	Low-Risk vs High-Risk Groups ^c	Low-Risk Group vs US White Population ^d
Women					
Incidence	463	618	789	25 (21-29)	41 (39-44)
Mortality	132	256	320	48 (44-53)	59 (55-62)
Men					
Incidence	283	425	759	33 (28-38)	63 (60-65)
Mortality	156	277	470	44 (39-48)	67 (64-69)

Abbreviation: PAR, population-attributable risk.

^a Total carcinomas include all cancers other than skin cancer, brain cancer, and neoplasms of lymphatic and hematopoietic tissues. Nonfatal prostate cancer is excluded in men. All rates are standardized based on the age distribution of the US population in 2000.

^b The US rate was obtained from the Surveillance, Epidemiology,

and End Results (SEER) program.^{25,26}

^c Calculated as the difference in the cancer rates between the low- and high-risk groups divided by the rate of the high-risk group.

^d Calculated as the difference in the cancer rates between the low-risk group and the national rate divided by the national rate.

paring our low-risk group with the white US population, we obtained a substantially higher PAR: 41% in women and 63% in men for incidence, and 59% in women and 67% in men for mortality.

We then assessed individual cancers (Figure 1 and Figure 2). Within our cohorts, the PARs for incident cancers in women and men, respectively, were 82% and 78% for lung, 29% and 20% for colon and rectum, 30% and 29% for pancreas, 36% and 44% for bladder, 36% and 4% for kidney, 16% and 38% for oral cavity and pharynx, 27% and 32% for liver, and 62% and 66% for esophagus. The PARs were 4% for breast cancer and 21% for endometrial, ovarian and fatal prostate cancer. A generally similar PAR was observed for cancer deaths except for a dramatic increase for some sites, including breast (12%), endometrium (49%), kidney in men (48%), and oral cavity and pharynx (75% in women and 57% in men).

When the low-risk group was compared with the US population, the resultant PARs were further increased. For example, the PAR rose to 15% for breast cancer incidence and 45% for mortality. For colorectal cancer, the PARs increased to 50% to 60% in both sexes. More detailed data are provided in eTable 2 in the Supplement.

Discussion

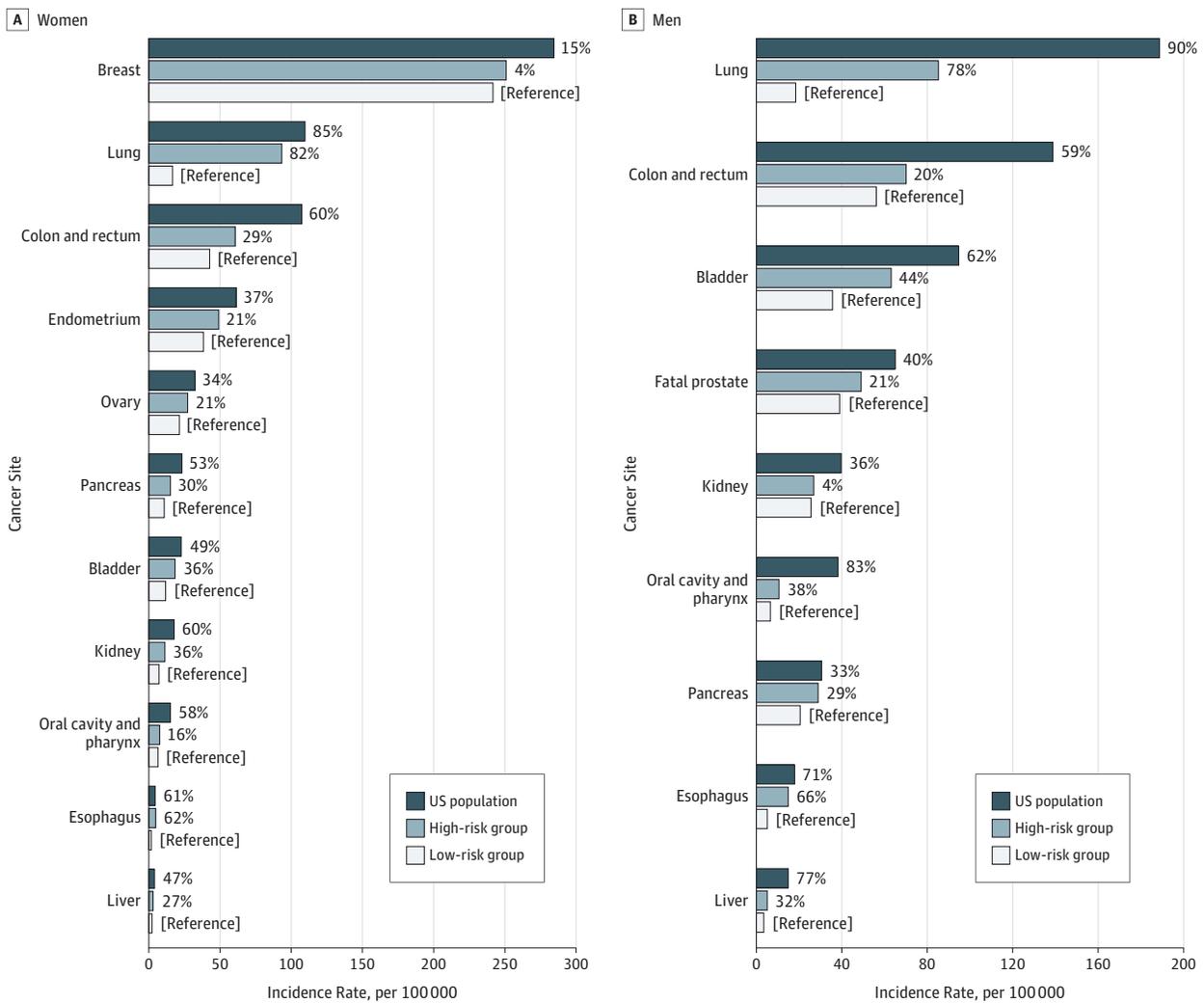
In the 2 cohort studies of US white individuals, we found that overall, 20% to 40% of carcinoma cases and about half of carcinoma deaths can be potentially prevented through lifestyle modification. Not surprisingly, these figures increased to 40% to 70% when assessed with regard to the broader US population of whites, which has a much worse lifestyle pattern than our cohorts. Notably, approximately 80% to 90% of lung cancer deaths could be avoided if Americans adopted the lifestyle of the low-risk group, mainly by quitting smoking. For other cancers, from 10% to 70% of deaths could be prevented. These results provide strong support for the importance of environmental factors in cancer risk and reinforce the enormous potential of primary prevention for cancer control.

The 4 factors considered in the current study are among the most prevalent lifestyle factors convincingly linked to various cancers. Smoking contributed to 48.5% of deaths from the 12 smoking-related cancers in the United States.²⁸ Heavy alcohol consumption has been causally related to increased risk of cancers in several sites, including colorectum, breast, oral cavity, pharynx, larynx, esophagus, and liver; and possibly to a higher risk of cancers of the lung, pancreas, stomach, and gallbladder.²⁹ Obesity increases risk of cancers in the esophagus (adenocarcinoma), colorectum, pancreas, breast (after menopause), endometrium, kidney, and liver; and probably increases risk of cancers in the ovaries, prostate (advanced only), and gallbladder.³ In contrast, physical activity has been linked to lower risk of cancers in the colorectum, breast, and endometrium.³

These compelling data together with the findings of the current study provide strong support for the argument that a large proportion of cancers are due to environmental factors and can be prevented by lifestyle modification.^{1,2} Although the stochastic effects of DNA replication error may contribute to the variation in cancer incidence across different tissues,⁴ these influences would be unlikely to explain the wide variation in cancer rates within tissues that have similar lifetime numbers of stem cell divisions or between individuals with different exposure profiles, or the rapidly increasing burden of cancer in low- and middle-income countries accompanying the global shifts in lifestyle and environmental exposures.^{8,30,31}

Several previous studies have attempted to quantify the contribution of environmental factors to cancer risk, with the estimated PAR ranging from 30% to 50%.³²⁻³⁴ A classic approach was often undertaken using the population prevalence of exposure and the relative risk estimate derived from the literature for each risk factor.³⁵ Therefore, several factors can contribute to the variation in PAR estimates, including differences in environmental factors considered in each study, varied definitions and prevalence of exposures, and different sources used to derive the relative risk estimates.

Figure 1. Cancer Incidence and the Corresponding Population-Attributable Risk (PAR) Estimates in the 2 Study Cohorts and the US White Population



A and B, The PAR estimates are reported as percentages, and the low-risk group serves as reference for both the general US white population and the high-risk groups.

In contrast, our study used the more straightforward approach of direct comparison of cancer rates between participants with distinct lifestyle profiles. This approach relies on detailed lifestyle and cancer follow-up data from 2 nationwide cohort studies and circumvents the need for derivation of relative risk estimates for each individual risk factor associated with each cancer. It also takes account of the joint contributions of multiple risk factors that are often difficult, if not impossible, to estimate by the classic approach owing to uncertainties about the interactions and complex relationships among risk factors.³⁶ This approach based on direct rather than derived data is similar to that used by Doll and Peto,³⁷ who compared US death rates with the lowest reliably observed death rates in other populations and estimated that about 75% of US cancer deaths could be attributed to lifestyle and other environmental factors.

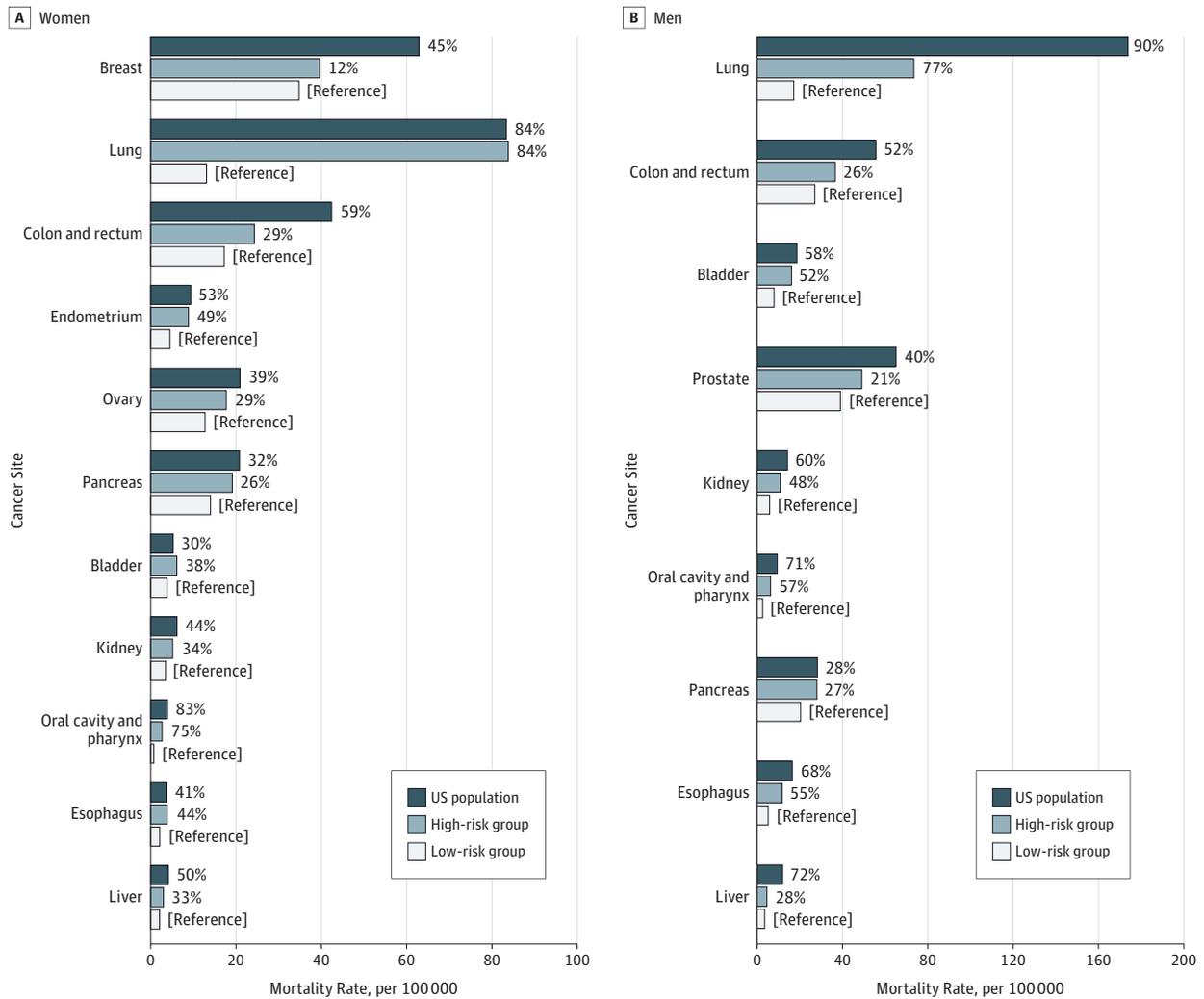
Our results are also consistent with a recent study showing that cell division-related intrinsic risk factors alone in the

absence of environmental risk factors do not confer substantial cancer risk.¹² Through mathematical modeling, that study demonstrates that accumulation of endogenous stem-cell mutation errors, estimated by assuming widely different mutation rates, is not sufficient to account for the observed cancer risk.¹² Taken together with our current empirical data, the 2 studies provide complementary evidence for the predominant role of extrinsic environmental factors in cancer risk.

However, it should be noted that we selected the 4 major lifestyle cancer risk factors for characterization of the low-risk group to show the preventable potential of cancer rather than to conclude causally that these were the only factors relevant to cancer risk. Therefore, the PARs that we calculated might include contributions from other behaviors that are closely related to the 4 specified lifestyle factors and that are also important determinants for cancer risk (eg, diet).

Moreover, we used a less stringent threshold for characterization of the low-risk profile to allow for a meaningful analy-

Figure 2. Cancer Mortality and the Corresponding Population-Attributable Risk (PAR) Estimates in the 2 Study Cohorts and the US White Population



A and B, The PAR estimates are reported as percentages, and the low-risk group serves as reference for both the general US white population and the high-risk groups.

sis for some less common cancers. For example, the upper limit for BMI was set at 27.5 rather than 25, as commonly used to define normal body weight. Thus, the potential preventability of cancer that can be achieved by primary prevention may be even higher than our estimates, especially considering other factors in the wider population, including occupational exposures, infectious agents, certain behaviors (eg, postmenopausal estrogen use), additional dietary factors, and early-life exposures.^{38,39}

It may be argued that the health professional backgrounds of the participants in our cohorts, especially those in the low-risk group, make them more health conscious and give them easier access to cancer screening and better treatment options than would be true in the general population; therefore, our PARs may have been overestimated. However, we did not find substantial difference between the 2 risk groups of our cohorts in the uptake of screening. For breast cancer, the rate of mammographic screening within the past 2 years, standard-

ized to the 2000 US population, was 78% in the high-risk group and 83% in the low-risk group in 2010. For colorectal cancer, the age-standardized rates in 2010 of ever having lower endoscopic screening in the high-risk and low-risk groups were 63% and 70% in women, and 68% and 75% in men, respectively. Although direct comparison with the US data are difficult because of the differences in assessment methods and time frames, these estimates are generally consistent with the overall US screening uptake,^{40,41} suggesting that screening is unlikely to have a substantial influence on our PAR estimates.

With regard to participants' health professional status potentially conferring access to better cancer therapy, the similar PAR estimates for cancer mortality (67%) and incidence (61%) in men argues against a strong influence of better therapy in our low-risk group relative to the general population—the reduction in cancer mortality was largely due to a reduction in incidence. In women, the PAR for mortality (59%) was substantially higher than for incidence (41%). Two main factors may

have contributed to this difference. First, smoking has a predominant effect that results in a much higher PAR for incident lung cancer than for breast cancer (85% vs 15%). Yet, despite its low incidence in women, lung cancer is much more fatal than breast cancer, thus contributing relatively more to the PAR for mortality than for incidence. Indeed, after excluding lung and breast cancers from total carcinoma, we obtained similar PARs for incidence and mortality in women (50% vs 48%). Second, the PAR for breast cancer was much higher for mortality (45%) than for incidence (15%), partly because mammographic screening actually increases cancer incidence due to detection of early or indolent cancer.⁴² In addition, some risk factors, such as obesity and physical inactivity, may influence survival by causing more aggressive cancers, increasing cancer progression, or making cancer more difficult to diagnose early and treat.⁴³⁻⁴⁵ Furthermore, the lifestyle risk factors lower incidence of comorbidities, such as cardiovascular disease and diabetes, which may affect cancer prognosis directly or indirectly (eg, by limiting aggressive therapy).⁴⁶

Finally, we only included whites in our PAR estimates, which may not be generalizable to other ethnic groups. However, all of the considered factors have been established as risk factors in diverse ethnic groups, although there could be differences in the magnitudes of the associations.

Conclusions

In conclusion, we found that a substantial proportion of cancer cases and even more deaths among US white individuals might be prevented by quitting smoking, avoiding heavy alcohol consumption, maintaining a BMI between 18.5 and 27.5, and exercising at a moderate intensity for at least 150 minutes or at a vigorous intensity for at least 75 minutes every week. These findings reinforce the predominant importance of lifestyle factors in determining cancer risk. Therefore, primary prevention should remain a priority for cancer control.

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Study concept and design: Song, Giovannucci.
Acquisition, analysis, or interpretation of data: Song, Giovannucci.
Drafting of the manuscript: Song.
Critical revision of the manuscript for important intellectual content: Song, Giovannucci.
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