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Article

ARTICLE

The Future Colorectal Cancer Burden Attributable to Modifiable Behaviors: A Pooled Cohort Study

Claire M. Vajdic, Robert J. MacInnis, Karen Canfell, Peter Hull, Maria E. Arriaga, Vasant Hirani, Robert G. Cumming, Paul Mitchell, Julie E. Byles, Graham G. Giles, Emily Banks, Anne W. Taylor, Jonathan E. Shaw, Dianna J. Magliano, Julie Marker, Barbara-Ann Adelstein, Tiffany K. Gill, Maarit A. Laaksonen

See the Notes section for the full list of authors' affiliations.
Correspondence to: Claire Vajdic, PhD, Centre for Big Data Research in Health, University of New South Wales, Level 1 AGSM Building, Sydney NSW 2052, Australia (e-mail: claire.vajdic@unsw.edu.au).

Abstract

Background: Previous estimates of the colorectal cancer (CRC) burden attributed to behaviors have not considered joint effects, competing risk, or population subgroup differences.
Methods: We pooled data from seven prospective Australian cohort studies ($n = 367\ 058$) and linked them to national registries to identify CRCs and deaths. We estimated the strength of the associations between behaviors and CRC risk using a parametric piecewise constant hazards model, adjusting for age, sex, study, and other behaviors. Exposure prevalence was estimated from contemporary National Health Surveys. We calculated population attributable fractions for CRC preventable by changes to current behaviors, accounting for competing risk of death and risk factor interdependence. Statistical tests were two-sided.
Results: During the first 10 years of follow-up, there were 3471 incident CRCs. Overweight or obesity explained 11.1%, ever smoking explained 10.7% (current smoking 3.9%), and drinking more than two compared with two or fewer alcoholic drinks per day explained 5.8% of the CRC burden. Jointly, these factors were responsible for 24.9% (95% confidence interval [CI] = 19.7% to 29.9%) of the burden, higher for men (36.7%) than women (13.2%, $P_{\text{difference}} < .001$). The burden attributed to these factors was also higher for those born in Australia (28.7%) than elsewhere (16.8%, $P_{\text{difference}} = .047$). We observed modification of the smoking-attributable burden by alcohol consumption and educational attainment, and modification of the obesity-attributable burden by age group and birthplace.
Conclusions: We produced up-to-date estimates of the future CRC burden attributed to modifiable behaviors. We revealed novel differences between men and women, and other high–CRC burden subgroups that could potentially benefit most from programs that support behavioral change and early detection.

Australia has a high incidence of colorectal cancer (CRC) (1). Ever smoking, being physically inactive, being overweight or obese, and consuming processed meat and excessive alcohol are established to increase CRC risk (2,3). Risk may also be increased by consuming red meat and inadequate whole grains, dietary fiber, and dairy. These behaviors often co-occur in individuals (4–9), and the burden related to one risk factor may be mediated by others. Typically, disease burden estimates do not take into account the simultaneous effects of other factors or the interdependence of effects, nor do they account for competing risk of death (10,11). To maximize their accuracy and policy relevance, population attributable fractions (PAFs) are

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Table 1. Characteristics of the individual and pooled cohort and representative external data sources

	Cohort data								External prevalence data	
Characteristic	MCCS	BMES	ALSWH	AusDiab	NWAHS	CHAMP	45&Up	Pooled	NHS	NDSHS
Baseline year(s)	1990–1994	1992–1993	1996	1999–2000	1999–2003	2005–2007	2006–2009	1990–2008	2014–2015	2013
Population, No.	41 328	3623	38 192	11 136	4012	1566	260 632	360 489	14 560	22 696
Incident CRC cases, No.*	600	80	397	133	40	40	2181	3471		
Deaths, No.*	2095	682	2575	779	280	416	13 313	20 140		
State/territory	VIC	NSW	All	All	SA	NSW	NSW	All	All	All
Age at baseline, mean (range), y	55 (27–76)	66 (45–97)	45† (18–75)	51 (25–91)	50 (18–90)	77 (70–96)	62 (45–>100)	59 (18–>100)	46 (18–85)	46 (18–84)
Women, %	59	57	100	55	52	0	54	59	51	51

*During the first 10 years of follow-up. 45&Up = 45 and Up Study; ALSWH = Australian Longitudinal Study on Women's Health; AusDiab = Australian Diabetes, Obesity and Lifestyle Study; BMES = Blue Mountains Eye Study; CHAMP = Concord Health and Ageing in Men Project; MCCS = Melbourne Collaborative Cohort Study; NDSHS = National Drug Strategy Household Survey; NHS = National Health Survey; NSW = New South Wales; NWAHS = North West Adelaide Health Study; SA = South Australia; VIC = Victoria.
†The ALSWH recruited three cohorts age 18–23, 45–50, and 70–75 years, so the age distribution is not continuous.

best estimated from prospective cohort studies (12) and up-to-date risk factor prevalence estimates representative of the population of interest.

We addressed this evidence gap by applying a comprehensive PAF method to an Australian cohort consortium and contemporaneous representative exposure prevalence data.

Methods

Study Population

We used individual-level data from the Australian cancer-PAF cohort consortium (13), which comprises the Melbourne Collaborative Cohort Study (MCCS) (14), Blue Mountains Eye Study (BMES) (15), Australian Longitudinal Study on Women's Health (ALSWH) (16), Australian Diabetes, Obesity and Lifestyle Study (AusDiab) (17), North West Adelaide Health Study (NWAHS) (18), Concord Health and Ageing in Men Project (CHAMP) (19), and the 45 and Up Study (45&Up) (20). The combined cohort sample was 369 515 adult Australians. The analytic sample was 360 489 individuals, after excluding 2457 who enrolled in more than one cohort, 1885 who did not consent to record linkage, and 4684 with a history of CRC (Table 1).

We obtained the most recent available risk factor prevalence estimates from the 2014–2015 National Health Survey (21) and the 2013 National Drug Strategy Household Survey (Table 1; Supplementary Table 1, available online) (22). The Australian Institute of Health and Welfare ethics committee approved the study (EC2013/4/62).

Data Harmonization

We examined modifiable behaviors with convincing or probable evidence of a causal association with CRC, as judged by expert review panels (2,3), if they were measured in our cohort and the national health surveys. These exposures were smoking, physical inactivity, body fatness (approximated by body mass index [BMI]), and excessive alcohol consumption at baseline (cohort entry). For smoking, we examined status, time since quitting (lag time, in decades), and intensity for current smokers. We could not estimate PAF for consumption of red or processed meat or inadequate consumption of whole grains, dietary fiber or dairy, as data on these exposures were not measured by the health surveys. We harmonized the exposures across the cohort studies and health surveys, classifying them in accordance with current Australian recommendations for healthy living, that is, not smoking, doing at least 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity per week, maintaining a healthy weight (BMI 18.5–25 kg/m^2), and drinking two or fewer alcoholic drinks per day (13). We also harmonized country of birth, marital status, educational attainment, socioeconomic status (23), and residential location (rurality) (24) (Supplementary Table 1, available online).

Data Linkage

We matched the pooled cohort to the Australian Cancer Database (25) and National Death Index to identify cancers and deaths using probabilistic linkage (26). These records were available until December 31, 2012, providing eight to 22 years of follow-up (Table 1).

Statistical Methods

We classified incident primary invasive CRCs of epithelial cell origin according to International Classification of Diseases for Oncology codes (ICD-O; C18-20), with subclassification to the colon (C18.0–18.9) and rectum (C19–20).

We defined follow-up as the time from baseline to the date of CRC diagnosis, death, or end of follow-up, whichever occurred first. We estimated the strength of the association between the behaviors and CRC and death using a parametric piecewise constant hazards model (27) and expressed them as hazard ratios (HR) with 95% confidence intervals (CIs). We restricted the analyses to the first 10 years of follow-up to generate comparable estimates across the cohorts and tested heterogeneity among the cohort-specific hazard ratios using the asymptotic DerSimonian and Laird Q statistic (28). In sensitivity analyses, we excluded the first 12 months of follow-up to evaluate the potential impact of reverse causality. We also adjusted our risk estimates by processed meat and red meat consumption, measured in the two largest cohorts, and CRC family history and screening, collected in the largest cohort.

We predefined two main effects models. The first model included age, sex, study, and each behavior separately. The second model included age, sex, study, and all behaviors statistically significantly associated with CRC. We computed the corresponding exposure prevalence (PR) estimates from the health surveys. We then combined the strength of the association and exposure prevalence estimates to calculate the PAF point estimates using our recently developed PAF formula (12). This formula defines PAF for cancer incidence as the expected excess cancer incidence during the follow-up time due to certain modifiable risk factors, while accounting for censoring due to death. This is done by comparing the probabilities that an individual is alive and disease-free given the original and modified risk factor values. The asymptotic variance estimate of PAF was obtained using the delta method, and two-sided 95% confidence intervals for PAFs were calculated by applying a symmetrizing complementary logarithmic transformation of PAF.

We calculated PAFs both for the individual and joint contributions of behaviors to the CRC burden. We evaluated scenarios in which the exposure was completely eliminated or only reduced. For example, we evaluated the scenario in which current or former smokers (eventually) had the same CRC risk as never smokers, and also the scenario in which current smokers of 20 or more cigarettes per day consumed instead fewer than 20 cigarettes per day. We estimated the number of Australian CRC cases that could be prevented by multiplying the PAF estimates by the projected numbers of CRCs over the next 10 years (2017–2026) (29).

We tested for potential effect modification of PAFs by other behaviors and sociodemographic factors. This was performed by including an interaction term between the risk factor and the potential effect-modifying factor in the model and by calculating the 95% confidence interval of the difference of the PAF estimates between the categories of the effect-modifying factor (30). The PAF difference between subgroups was deemed statistically significant if the *P* value for the difference was less than .05. We also calculated PAFs by CRC topography and using the traditional PAF method (11).

We carried out all statistical analyses using SAS 9.4 (SAS Institute, Inc., Cary, NC) and our publicly available PAF program based on SAS macros (31). All statistical tests were two-sided.

Results

We observed 3471 incident CRCs and 20 140 deaths during the first 10 years of follow-up (Table 1).

CRC Behavioral Risk Factors

We found no heterogeneity among the cohort-specific hazard ratios of CRC in relation to behaviors (Supplementary Table 2, available online).

Taking men and women together, CRC risk was positively associated with smoking, overweight and obesity (BMI $\geq$25 kg/m^2), and excessive alcohol consumption but was not associated with physical inactivity in the multivariable-adjusted model (Table 2). The risk for former smokers was virtually identical to that for current smokers, and for former smokers the risk was elevated up to 40 years after cessation. In terms of current smoking frequency, only those who smoked 20 or more cigarettes per day were at increased risk. The strength of these associations was modest at most and did not materially change after excluding the first 12 months of follow-up or in subset analyses adjusted for consumption of processed meat or red meat, or CRC family history or screening (data not shown). The associations were also largely unchanged after adjustment for country of birth, educational attainment, socioeconomic status, and residential location (Supplementary Table 3, available online). The findings were broadly similar for colon and rectal cancers (Supplementary Tables 4 and 5, available online).

The hazard ratios for risk factors stratified by each other are shown in Table 3. Overall, 40% of individuals (50% men, 29% women) had at least two of the three behavioral risk factors.

Competing Risk of Death

Smoking, underweight, and obesity (BMI $\geq$30 kg/m^2) increased the risk of death, whereas excessive alcohol consumption and overweight (BMI 25–$<$30 kg/m^2) were inversely associated (Supplementary Table 6, available online).

CRC Burden

Individual Behaviors

We found that the CRC burden for men and women attributable to ever smoking was 10.7%, and that attributable to current smoking was 3.9%; given the extended excess risk for former smokers, these correspond to the burdens avoidable over a 50-year time frame (Table 2). Of the burden for current smokers, 1.3% could be prevented if those smoking 20 or more cigarettes per day were to smoke fewer than 20 cigarettes per day.

Our estimate for the CRC burden attributable to overweight or obesity (BMI $\geq$25 kg/m^2) was 11.1%, of which obesity explained 7.7% (Table 2). Our modeling predicts that 5.0%, or up to 9100 CRCs in Australia in the next 10 years, would be prevented if all obese individuals were overweight.

Excessive alcohol consumption contributed 5.8% of the burden (Table 2), or up to 10 600 preventable CRCs over the next 10 years. The CRC burden attributable to physical inactivity was not statistically significant (data not shown).

Joint Behaviors

We estimated that ever smoking, BMI of 25 kg/m^2 or greater, and excessive alcohol consumption jointly explain 24.9% of the future CRC burden for men and women (Table 2). Quitting smoking, reaching a healthy weight, and not drinking excessively could reduce 19.4% or up to 35 400 CRC cases over the next 10 years.

Population Subgroups

We found PAF effect modification by sex. The burdens attributable to a BMI of 25 kg/m^2 or greater and excessive alcohol consumption were higher for men than women, as were the joint contributions of smoking, excess body weight, and excess alcohol (Table 2).

We found PAF effect modification between smoking and alcohol (Table 3). The CRC burden attributable to smoking and to excessive alcohol was higher in the presence of the other exposure.

The PAF attributable to obesity was higher for those younger than 75 years than those 75 years or older. The burden attributable to a BMI of 25 kg/m^2 or greater, and the burden attributable to the joint effects of ever smoking, BMI of 25 kg/m^2 or greater, and excessive alcohol consumption, was also higher for Australian-born participants compared with migrants (Table 4). We found PAF effect modification between smoking (ever or current) and education, with excess smoking-related risk and burden of CRC for people of high, but not low, educational attainment. We found no trends in CRC burden attributable to smoking, a BMI of 25 kg/m^2 or greater, or excess alcohol by

Table 2. Exposure prevalence, hazard ratios for CRC incidence by exposure level, and fractions of CRC incidence attributable to exposure to behavioral risk factors over 10 years of follow-up

	Prevalence, %			HR (95% CI)*			
Behavioral risk factor	All	Men	Women	All	Men	Women	P†
Smoking status							
1. Never smoker	53	45	60	1	1	1	
2. Former smoker	31	36	27	1.23 (1.14 to 1.33)	1.25 (1.12 to 1.39)	1.22 (1.09 to 1.36)	
3. Current smoker	16	19	13	1.26 (1.10 to 1.44)	1.30 (1.07 to 1.57)	1.23 (1.02 to 1.49)	
PAF (2–3 → 1)				10.7 (6.8 to 14.4)	13.0 (6.7 to 18.9)	8.4 (3.8 to 12.7)	.22
PAF (2 → 1)				6.8 (4.3 to 9.3)	8.0 (4.1 to 11.8)	5.5 (2.3 to 8.6)	.33
PAF (3 → 1)				3.9 (1.4 to 6.3)	5.0 (1.0 to 8.9)	2.8 (0.01 to 5.6)	.37
Current smoking frequency							
1. Never	56	52	61	1	1	1	
Former smoker, who quit:							
2. 40+ y ago	2	3	1	0.98 (0.82 to 1.16)	0.99 (0.81 to 1.22)	0.98 (0.71 to 1.36)	
3. 30–39 y ago	3	4	3	1.15 (1.00 to 1.33)	1.13 (0.94 to 1.35)	1.22 (0.96 to 1.54)	
4. 20–29 y ago	5	5	5	1.20 (1.06 to 1.36)	1.22 (1.03 to 1.43)	1.19 (0.98 to 1.45)	
5. 10–19 y ago	6	6	6	1.30 (1.15 to 1.47)	1.38 (1.17 to 1.63)	1.19 (0.97 to 1.45)	
6. <10 y ago	10	10	10	1.46 (1.28 to 1.66)	1.52 (1.27 to 1.81)	1.40 (1.15 to 1.70)	
Current smoker, cigs/d							
7. 0–19	14	16	11	1.11 (0.91 to 1.36)	1.20 (0.89 to 1.60)	1.06 (0.81 to 1.37)	
8. ≥20	4	5	4	1.45 (1.21 to 1.74)	1.43 (1.22 to 1.83)	1.51 (1.17 to 1.96)	
PAF (8 → 7)				1.3 (0.03 to 2.6)	1.0 (–1.0 to 3.1)	1.5 (–0.01 to 3.0)	.73
BMI, kg/m^2							
1. <18.5	2	1	2	1.04 (0.78 to 1.40)	1.28 (0.74 to 2.22)	0.93 (0.66 to 1.33)	
2. 18.5–24.9	35	28	42	1	1	1	
3. 25.0–29.9	36	42	29	1.11 (1.02 to 1.20)	1.27 (1.13 to 1.44)	0.97 (0.87 to 1.09)	
4. ≥30.0	28	28	27	1.30 (1.19 to 1.44)	1.49 (1.29 to 1.72)	1.18 (1.03 to 1.34)	
PAF (3–4 → 2)				11.1 (6.4 to 15.6)	20.4 (13.1 to 27.1)	4.0 (–1.9 to 9.5)	<.001
PAF (3 → 2)				3.4 (0.6 to 6.2)	9.2 (4.7 to 13.5)	–0.7 (–3.9 to 2.4)	<.001
PAF (4 → 2)				7.7 (4.8 to 10.4)	11.2 (7.1 to 15.1)	4.7 (0.9 to 8.4)	.02
PAF (4 → 3)				5.0 (2.1 to 7.7)	4.9 (0.8 to 8.9)	5.4 (1.4 to 9.2)	.88
Alcohol consumption, drinks/d							
1. ≤2	81	71	90	1	1	1	
2. >2	19	29	10	1.32 (1.20 to 1.46)	1.37 (1.22 to 1.53)	1.15 (0.94 to 1.42)	
PAF (2 → 1)				5.8 (3.7 to 7.9)	9.0 (5.6 to 12.3)	1.5 (–0.8 to 3.7)	<.001
Physical activity, min/wk							
1. ≥150	26	31	21	1	1	1	
2. <150	74	69	79	1.02 (0.93 to 1.12)	0.98 (0.87 to 1.11)	1.07 (0.93 to 1.23)	
Joint behaviors							
PAF: ever smoking, BMI ≥25 kg/m^2, and >2 alcoholic drinks/d				24.9 (19.7 to 29.9)	36.7 (29.2 to 43.4)	13.2 (6.0 to 19.8)	<.001
PAF: current smoking, BMI ≥25 kg/m^2, and >2 alcoholic drinks/d				19.4 (14.3 to 24.2)	31.1 (23.7 to 37.7)	8.1 (1.3 to 14.3)	<.001

*Adjusted for age, sex, study, smoking, body mass index, and alcohol consumption. Some percentages do not add up to 100 because of rounding. BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; PAF = population attributable fraction.
†P value for difference in PAF estimates between men and women.

socioeconomic status, and no variation in relation to residential location or marital status (data not shown).

Colon and Rectal Cancer Burden

PAF estimates for colon cancer and rectal cancer were broadly similar to those for all CRCs (Supplementary Tables 4 and 5, available online).

Traditional PAF Method

PAF estimates using our method and the traditional approach were largely similar (Supplementary Table 7, available online).

Discussion

One-quarter of Australian CRCs are attributable to the combined effects of ever smoking, being overweight or obese, and drinking excessive alcohol. We showed that adopting healthy living recommendations with respect to these behaviors is likely to produce a marked reduction of the CRC burden for men but a relatively modest reduction for women. We found that the burden of CRC attributed to smoking persists for four decades after quitting, reinforcing the importance of preventing smoking initiation, in addition to measures encouraging smoking cessation. Nevertheless, our data indicate that the future CRC burden would be markedly lower if current and former smokers did not

Table 3. Exposure prevalence, hazard ratios for CRC incidence by exposure level, and fractions of CRC incidence attributable to exposure to behavioral risk factors by other behavioral risk factors

Effect modifier	Subgroup 1		Subgroup 2		Subgroup 3		
Behavioral risk factor	PR, %	HR (95% CI)*	PR, %	HR (95% CI)*	PR, %	HR (95% CI)*	P†
Smoking status	Never smoker		Former smoker		Current smoker		
BMI, kg/m^2							
1. <18.5	2	0.89 (0.57 to 1.39)	1	1.19 (0.73 to 1.93)	2	1.22 (0.62 to 2.41)	
2. 18.5–24.9	39	1	27	1	38	1	
3. 25.0–29.9	34	1.16 (1.04 to 1.30)	39	1.04 (0.92 to 1.18)	34	1.12 (0.85 to 1.47)	
4. ≥30	25	1.40 (1.22 to 1.60)	34	1.25 (1.08 to 1.44)	26	1.02 (0.72 to 1.46)	
PAF (3, 4 → 2)		13.5 (7.4 to 19.2)		9.1 (0.6 to 16.8)		4.4 (–12.2 to 18.5)	$P_{1\text{-}2} = .38$, $P_{1\text{-}3} = .27$, $P_{2\text{-}3} = .59$
PAF (4 → 3)		5.1 (1.4 to 8.7)		6.3 (1.3 to 11.0)		–2.3 (–12.1 to 6.6)	$P_{1\text{-}2} = .71$, $P_{1\text{-}3} = .15$, $P_{2\text{-}3} = .11$
Alcohol consumption, drinks/d							
1. ≤2	90	1	77	1	69	1	
2. >2	10	1.15 (0.96 to 1.38)	23	1.37 (1.21 to 1.55)	31	1.55 (1.19 to 2.03)	
PAF (2 → 1)		1.6 (–0.6 to 3.6)		8.1 (4.7 to 11.5)		15.0 (4.8 to 24.1)	$P_{1\text{-}2} = .001$, $P_{1\text{-}3} < .001$, $P_{2\text{-}3} = .19$
BMI, kg/m^2	18.5–24.9		25.0–29.9		≥30		
Smoking status							
1. Never	58	1	51	1	47	1	
2. Former	24	1.31 (1.15 to 1.49)	34	1.18 (1.05 to 1.33)	38	1.19 (1.01 to 1.38)	
3. Current	17	1.34 (1.08 to 1.66)	15	1.30 (1.05 to 1.61)	15	0.99 (0.72 to 1.36)	
PAF (2, 3 → 1)		12.4 (6.4 to 18.1)		10.2 (3.9 to 16.0)		6.5 (–2.3 to 14.5)	$P_{1\text{-}2} = .60$, $P_{1\text{-}3} = .25$, $P_{2\text{-}3} = .48$
PAF (3 → 1)		5.5 (1.1 to 9.8)		4.4 (0.4 to 8.2)		–0.2 (–4.9 to 4.3)	$P_{1\text{-}2} = .69$, $P_{1\text{-}3} = .07$, $P_{2\text{-}3} = .13$
Alcohol consumption, drinks/d							
1. ≤2	84	1	80	1	82	1	
2. >2	15	1.34 (1.13 to 1.59)	20	1.34 (1.17 to 1.54)	18	1.27 (1.04 to 1.55)	
PAF (2 → 1)		5.5 (2.0 to 8.9)		6.8 (3.3 to 10.1)		4.9 (0.4 to 9.5)	$P_{1\text{-}2} = .61$, $P_{1\text{-}3} = .84$, $P_{2\text{-}3} = .51$
Alcohol consumption, drinks/d	≤2		>2				
Smoking status							
1. Never	58	1	29	1			
2. Former	29	1.21 (1.11 to 1.31)	42	1.43 (1.17 to 1.74)			
3. Current	13	1.18 (1.01 to 1.39)	29	1.59 (1.20 to 2.11)			
PAF (2, 3 → 1)		8.0 (4.3 to 11.6)		25.8 (12.8 to 36.8)			$P_{1\text{-}2} = .005$
PAF (3 → 1)		2.3 (–0.04 to 4.5)		12.4 (4.3 to 19.8)			$P_{1\text{-}2} = .01$
BMI, kg/m^2							
1. <18.5	2	1.05 (0.77 to 1.43)	1	1.02 (0.42 to 2.48)			
2. 18.5–24.9	36	1	31	1			
3. 25.0–29.9	35	1.11 (1.01 to 1.21)	40	1.09 (0.89 to 1.32)			
4. ≥30	28	1.32 (1.19 to 1.47)	29	1.22 (0.96 to 1.54)			
PAF (3, 4 → 2)		11.5 (6.4 to 16.3)		8.8 (–4.1 to 20.1)			$P_{1\text{-}2} = .69$
PAF (4 → 3)		5.3 (2.2 to 8.4)		3.4 (–3.4 to 9.7)			$P_{1\text{-}2} = .60$

*Adjusted for age, sex, study, smoking, BMI, and alcohol consumption. Some percentages do not add up to 100 because of rounding. BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; PAF = population attributable fraction; PR = prevalence.

†P value for difference in PAF estimates between subgroups.

drink excessive alcohol. We also identified other inequalities in the population-level burden of CRC that may guide cancer control activities.

Our CRC PAF estimates are not directly comparable to previous estimates because they are based on different populations, time periods, and analytical approaches, including Australian PAF estimates for 2010: 6.4% for ever smoking, 9.0% for overweight and obesity, 9.0% for excessive alcohol consumption, and 4.8% for physical inactivity (32).

Based on current exposure prevalence, and consistent with prior large-scale cohort studies, we found that tobacco smoking (33–35), excess body weight (35–38), and excessive alcohol consumption (33,35,39,40) each contributed statistically significantly to the burden of CRC or colon cancer. Smoking is a major modifiable risk factor for CRC, with cases attributed to smoking up to 40 years after stopping, in accordance with previous lag time estimates (41,42). Critically, smokers are less likely than nonsmokers to participate in CRC screening (43–46). Our data

Table 4. Exposure prevalence, hazard ratios for CRC incidence by exposure level, and fractions of CRC incidence attributable to exposure to behavioral risk factors by sociodemographic factors

Effect modifier	Subgroup 1		Subgroup 2		Subgroup 3		
Behavioral risk factor	PR, %	HR (95% CI)*	PR, %	HR (95% CI)*	PR, %	HR (95% CI)*	P†
Age group, y		<65		65–74		≥75	
Smoking status							
1. Never	53	1	47	1	52	1	
2. Former	29	1.33 (1.18 to 1.51)	44	1.19 (1.06 to 1.34)	44	1.14 (0.98 to 1.33)	
3. Current	18	1.29 (1.07 to 1.55)	9	1.23 (0.98 to 1.54)	4	1.44 (0.94 to 2.20)	
PAF (2, 3 → 1)		13.4 (7.3 to 19.0)		9.9 (3.6 to 15.8)		7.5 (–0.3 to 14.7)	P_{1-2} = .42, P_{1-3} = .22, P_{2-3} = .62
PAF (3 → 1)		4.8 (1.0 to 8.4)		1.9 (–0.3 to 4.1)		1.5 (–0.6 to 3.6)	P_{1-2} = .20, P_{1-3} = .14, P_{2-3} = .80
BMI, kg/m^2							
1. <18.5	2	1.15 (0.63 to 2.10)	0	1.20 (0.77 to 1.88)	2	0.89 (0.53 to 1.49)	
2. 18.5–24.9	37	1	25	1	29	1	
3. 25.0–29.9	34	1.11 (0.97 to 1.28)	39	0.99 (0.87 to 1.12)	42	1.21 (1.03 to 1.42)	
4. ≥30	27	1.33 (1.15 to 1.55)	35	1.24 (1.07 to 1.44)	27	1.11 (0.88 to 1.40)	
PAF (3, 4 → 2)		11.6 (3.7 to 18.8)		7.3 (–1.6 to 15.5)		10.8 (0.3 to 20.3)	P_{1-2} = .47, P_{1-3} = .91, P_{2-3} = .60
PAF (4 → 3)		5.4 (1.1 to 9.6)		8.4 (3.0 to 13.5)		–2.3 (–8.8 to 3.7)	P_{1-2} = .39, P_{1-3} = .04, P_{2-3} = .01
Alcohol consumption, drinks/d							
1. ≤2	82	1	81	1	89	1	
2. >2	18	1.33 (1.15 to 1.54)	19	1.28 (1.10 to 1.49)	11	1.25 (0.995 to 1.57)	
PAF (2 → 1)		6.1 (2.7 to 9.3)		5.4 (1.8 to 8.9)		2.9 (–0.3 to 6.0)	P_{1-2} = .78, P_{1-3} = .17, P_{2-3} = .29
Joint behaviors							
PAF: ever smoking, BMI ≥25 kg/m^2, and >2 alcoholic drinks/d		27.7 (19.3 to 35.1)		20.8 (11.3 to 29.4)		19.8 (8.1 to 30.0)	P_{1-2} = .26, P_{1-3} = .25, P_{2-3} = .88
Educational attainment		Low		Intermediate		High	
Smoking status							
1. Never	49	1	46	1	67	1	
2. Former	31	1.12 (1.01 to 1.25)	36	1.27 (1.10 to 1.47)	26	1.48 (1.23 to 1.77)	
3. Current	20	1.07 (0.90 to 1.28)	19	1.32 (1.00 to 1.73)	7	2.19 (1.58 to 3.03)	
PAF (2, 3 → 1)		5.3 (–0.5 to 10.8)		13.8 (5.3 to 21.6)		17.8 (10.7 to 24.3)	P_{1-2} = .09, P_{1-3} = .01, P_{2-3} = .47
PAF (3 → 1)		1.4 (–2.4 to 5.2)		5.3 (–0.4 to 10.7)		7.2 (3.2 to 10.9)	P_{1-2} = .26, P_{1-3} = .04, P_{2-3} = .58
BMI, kg/m^2							
1. <18.5	2	1.01 (0.69 to 1.49)	1	1.12 (0.61 to 2.05)	2	1.11 (0.52 to 2.36)	
2. 18.5–24.9	34	1	31	1	42	1	
3. 25.0–29.9	34	1.04 (0.93 to 1.16)	37	1.24 (1.06 to 1.45)	36	1.15 (0.95 to 1.40)	
4. ≥30	30	1.26 (1.11 to 1.42)	31	1.40 (1.16 to 1.69)	21	1.20 (0.93 to 1.55)	
PAF (3, 4 → 2)		8.3 (1.7 to 14.3)		17.8 (8.0 to 26.5)		9.1 (–1.6 to 18.7)	P_{1-2} = .09, P_{1-3} = .89, P_{2-3} = .21
PAF (4 → 3)		6.1 (2.1 to 9.9)		4.1 (–2.1 to 9.9)		1.0 (–4.9 to 6.5)	P_{1-2} = .58, P_{1-3} = .14, P_{2-3} = .46
Alcohol consumption, drinks/d							
1. ≤2	83	1	79	1	86	1	
2. >2	17	1.38 (1.20 to 1.58)	21	1.29 (1.08 to 1.54)	14	1.23 (0.99 to 1.52)	
PAF (2 → 1)		6.3 (3.4 to 9.2)		6.1 (1.5 to 10.5)		3.6 (–0.5 to 7.4)	P_{1-2} = .95, P_{1-3} = .27, P_{2-3} = .39
Joint behaviors							
PAF: ever smoking, BMI ≥25 kg/m^2, and >2 alcoholic drinks/d		18.4 (10.5 to 25.6)		33.3 (22.8 to 42.3)		27.5 (16.9 to 36.7)	P_{1-2} = .02, P_{1-3} = .15, P_{2-3} = .41
Country of birth		Australia		Elsewhere			
Smoking status							
1. Never	50	1	58	1			
2. Former	32	1.26 (1.15 to 1.38)	30	1.17 (0.999 to 1.37)			
3. Current	18	1.28 (1.09 to 1.51)	12	1.33 (1.03 to 1.72)			
PAF (2, 3 → 1)		12.3 (7.4 to 16.6)		9.0 (1.7 to 15.7)			P_{1-2} = .45
PAF (3 → 1)		4.5 (1.3 to 7.7)		4.0 (0.1 to 7.8)			P_{1-2} = .83

(continued)

Table 4. (continued)

Effect modifier	Subgroup 1		Subgroup 2		Subgroup 3		
Behavioral risk factor	PR, %	HR (95% CI)*	PR, %	HR (95% CI)*	PR, %	HR (95% CI)*	P†
BMI, kg/m^2							
1. <18.5	2	1.11 (0.79 to 1.55)	2	0.81 (0.40 to 1.63)			
2. 18.5–24.9	34	1	38	1			
3. 25.0–29.9	34	1.12 (1.02 to 1.24)	38	1.05 (0.89 to 1.24)			
4. ≥30	30	1.41 (1.26 to 1.57)	23	1.06 (0.87 to 1.40)			
PAF (3, 4 → 2)		14.4 (8.9 to 19.6)		3.2 (–6.8 to 12.3)			$P_{1\text{-}2} = .045$
PAF (4 → 3)		7.4 (3.8 to 10.8)		0.4 (–4.3 to 4.8)			$P_{1\text{-}2} = .02$
Alcohol consumption, drinks/d							
1. ≤2	80	1	88	1			
2. >2	20	1.27 (1.14 to 1.42)	12	1.49 (1.22 to 1.81)			
PAF (2 → 1)		5.6 (2.8 to 8.3)		6.0 (2.6 to 9.2)			$P_{1\text{-}2} = .87$
Joint behaviors							
PAF: ever smoking, BMI ≥25 kg/m^2, and >2 alcoholic drinks/d		28.7 (22.6 to 34.4)		16.8 (5.9 to 26.5)			$P_{1\text{-}2} = .047$

*Adjusted for age, sex, study, smoking, BMI, and alcohol consumption. Some percentages do not add up to 100 because of rounding. BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; PAF = population attributable fraction; PR = prevalence.
†P value for difference in PAF estimates between subgroups.

add to the compelling case for ongoing and new tobacco control initiatives and programs that promote CRC screening participation by smokers.

To our knowledge, we are the first to formally test differences of PAF estimates by subgroup, including by sex. We found a higher CRC burden attributable to overweight or obesity and excessive alcohol for men compared with women. These differences in burden appeared to be due to differences in both exposure prevalence and magnitude of the risk. This is consistent with prior evidence showing a higher CRC risk associated with excess BMI for men compared with women (47,48). Although prior PAF estimates for men and women have not been compared statistically, they align with our findings (35,38). Sex hormones (49–51) and related differences in body fat distribution, in particular abdominal adiposity (52), appear likely to contribute to the sex disparity. Together with the global trajectory of increasing BMI (53), our findings make a case to support men, in particular, achieving and maintaining a healthy weight to prevent CRC. Regarding excessive alcohol consumption, it has long been appreciated that men drink more alcohol than women, and meta-analyses have identified higher CRC risk associated with moderate or heavy consumption for men compared with women (54,55). Increasing recognition of the contribution of alcohol to the cancer burden has led to calls for multifaceted public health strategies designed to prevent people from starting drinking and to reduce high-risk consumption (56). Our results suggest that these efforts may need to be especially targeted to current and former smokers.

Given the clustering of unhealthy behaviors in individuals and the complex interelated pathophysiologic changes associated with coexisting behaviors, burden estimates stratified by other behaviors are essential to addressing residual confounding and reverse causation (57). Using this approach, we revealed that the burden attributable to ever smoking was exacerbated by excessive alcohol consumption, and vice-versa. The only previous study found no evidence of interaction based on a small number of CRCs (33). In support of our observations, strong interactions between smoking and alcohol use have been identified by risk factor studies for cancers of the upper aerodigestive tract (58–60). Adjustment for screening did not affect estimates for smoking or alcohol, in either the main or interaction analyses.

Subgroups that bear the greatest future burden have the most to gain from effective strategies aimed at modifying unhealthy behaviors and encouraging early detection. The only sociodemographic characteristic we found to mediate the CRC burden attributable to smoking was educational attainment, and it was driven by a lack of association between CRC risk and smoking for those with low educational attainment. Two European cohorts observed a positive association between CRC or colon cancer risk and education level (61,62), but only one was robust to full adjustment (61). This finding requires confirmation and investigation of the underlying cause. Interestingly, we saw no PAF modification by socioeconomic status.

In addition to sex, other sociodemographic factors mediated the CRC burden attributable to excess body weight. PAFs were higher for those younger than 75 years compared with those 75 years or older and the Australian-born compared with migrants; again, the differences were driven by differences in risk rather than prevalence. A higher incidence of CRC in Australian-born people compared with migrants has been documented (63) but not attributed to differences in BMI. Our results add to the existing strong case for continued public health campaigns promoting the health benefits of avoiding weight gain, and they could be used to guide personalized cancer prevention programs.

Physical activity was not associated with CRC risk in our cohort, although we had reduced statistical power to examine this at most modest protective association, with only four cohorts having harmonizable data. The World Cancer Research Fund classifies the evidence supporting this association as convincing but also acknowledges moderate heterogeneity between studies and no association with rectal cancer (2).

Our study was strengthened by several design features. First, we matched the strength of association estimates from prospective cohort data with contemporary, representative exposure prevalence estimates. Second, we used a PAF method that accounted for the simultaneous effects of risk factors and their modification both on CRC incidence and death, and generated 95% confidence intervals for the PAF estimates. Together, these features maximized the accuracy and generalizability of our PAF estimates, and they allowed us to perform risk factor interaction and population subgroup analyses that identified statistically significant differences in CRC burden. The high prevalence of coexisting harmful behaviors across industrialized countries (6–9) supports the generalizability of this analytical approach.

As one established and several probable lifestyle risk factors were not measured by the national health surveys, we could not assess their contribution to CRC burden. Reassuringly, risk estimates for smoking, BMI, and alcohol remained statistically significant when we adjusted for processed and red meat consumption in the two cohorts that ascertained these exposures. Although we pooled multiple prospective cohorts with individual-level data, our power remained limited for some analyses, particularly those assessing effect modification. We also acknowledge that we only considered exposures measured at baseline, and they may have changed during follow-up. Relatively large changes in the population-level prevalence of BMI have been observed over time (13), and such changes are likely to bias our risk and PAF estimates toward the null. It is also worth noting that PAF estimation assumes immediate risk reduction following the hypothetical exposure modification. In reality, risk reduction is likely to be gradual, as we demonstrated for smoking and CRC risk, but there are no data on CRC risk reduction after healthy changes in BMI and alcohol consumption.

In summary, we have shown that a large proportion of CRC is potentially preventable by behavior modification, particularly for men. We used a novel PAF method to generate precise estimates of the behavioral factors contributing to the future burden of CRC, the highest burden behavior combinations, and the highest burden subgroups. This information can inform both general and targeted education, public policy, health literacy, and health promotion campaigns aimed at reducing cancer incidence and maximizing early detection.

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Notes

Affiliations of authors: Centre for Big Data Research in Health (CMV, PH, MEA, MAL) and Prince of Wales Clinical School (KC, BAA), University of New South Wales, Sydney, Australia; Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, Australia (RJM, GGG); Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia (RJM, GGG); Cancer Research Division, Cancer Council New South Wales, Sydney, Australia (KC); School of Public Health (KC, VH, RGC), School of Life and Environmental Sciences, Charles Perkins Centre (VH), and Centre for Vision Research, Westmead Institute for Medical Research (PM), University of Sydney, Sydney, Australia; ANZAC Research Institute, University of Sydney and Concord Hospital, Sydney, Australia (RGC); Research Centre for Gender, Health and Ageing, University of Newcastle, Newcastle, Australia (JEB); ANU College of Medicine, Biology and Environment, Australian National University, Canberra, Australia (EB); Adelaide Medical School, University of Adelaide, Adelaide, Australia (AWT, TKG); Clinical Diabetes Laboratory (JES) and Diabetes and Population Health Laboratory (DJM), Baker Heart and Diabetes Institute, Melbourne, Australia; Cancer Voices South Australia, Adelaide, Australia (JM).

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