Alcohol Intake in Early Adulthood and Risk of Colorectal Cancer: Three Large Prospective Cohort Studies of Men and Women in the United States

Jinhee Hur, PhD[1], Stephanie A. Smith-Warner, PhD[1,2], Eric B. Rimm, ScD[1-3], Walter C. Willett, MD, DrPH[1-3], Kana Wu, MD, PhD[1†], Yin Cao, ScD, MPH[4,5†], Edward Giovannucci, MD, ScD[1-3†*]

[1] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[2] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[3] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[4] Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA
[5] Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA

[†] Contributed equally as senior authors

Correspondence to: Edward Giovannucci, MD, ScD, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, Boston, MA 02115, USA (Email: egiovann@hsph.harvard.edu)

Supplementary Table 1 Distribution of alcohol intake in early adulthood in the NHS, NHSII and HPFS

	Alcohol intake in early adulthood, g/day	
	Mean (standard deviation)	Range
NHS	2.5 (3.6)	0 to 32.0
NHSII	5.0 (7.9)	0 to 76.8
HPFS	4.7 (6.6)	0 to 32.0

Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II

Supplementary Table 2 Alcohol intake in early adulthood and risk of colorectal cancer with additional adjustment for risk factors in mid-adulthood[a]

	Alcohol intake in early adulthood, g/day				*P* for trend[b]	*P* for heterogeneity[c]
	0	0.1-4.9	5-14.9	≥15		
Pooled						
Multivariable model 1 HR (95% CI)[d]	1	1.05 (0.94 to 1.18)	1.07 (0.94 to 1.21)	1.20 (0.92 to 1.56)	0.09	0.32
Multivariable model 2 HR (95% CI)[e]	1	1.07 (0.97 to 1.18)	1.08 (0.95 to 1.22)	1.20 (0.92 to 1.57)	0.08	0.39
NHS						
Multivariable model 1 HR (95% CI)[d]	1	1.10 (0.97 to 1.25)	1.17 (0.96 to 1.41)	1.71 (0.90 to 3.22)	0.02	
Multivariable model 2 HR (95% CI)[e]	1	1.11 (0.98 to 1.25)	1.16 (0.96 to 1.40)	1.61 (0.85 to 3.05)	0.04	
NHSII						
Multivariable model 1 HR (95% CI)[d]	1	1.17 (0.88 to 1.55)	1.02 (0.76 to 1.36)	1.30 (0.72 to 2.36)	0.63	
Multivariable model 2 HR (95% CI)[e]	1	1.18 (0.89 to 1.57)	1.04 (0.77 to 1.39)	1.37 (0.76 to 2.49)	0.52	
HPFS						
Multivariable model 1 HR (95% CI)[d]	1	0.95 (0.82 to 1.11)	1.00 (0.81 to 1.22)	1.06 (0.76 to 1.47)	0.58	
Multivariable model 2 HR (95% CI)[e]	1	0.98 (0.84 to 1.14)	1.01 (0.82 to 1.23)	1.06 (0.76 to 1.49)	0.62	

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II

[a] Covariates listed in the footnote of Table 2 were included in models: **race** (white, nonwhite), **height** (continuous), **BMI in early adulthood** (at age 18 for NHS and NHSII; at age 21 for HPFS [continuous]), **pack-years of smoking before age 30** (continuous) and **physical activity at age 18-22** (in metabolic equivalent of task-hours/week for NHSII [continuous]; strenuous physical activity ≥2 times/week, 10-12 months/year for NHS and HPFS [yes, no]).

[b] Test for trend was performed using the median of each category of alcohol intake in early adulthood as a continuous variable.

[c] Cochran's Q test was used to test heterogeneity of the trend across the studies.

[d] Additionally adjusted for **cumulative alcohol intake in mid-adulthood** (continuous).

[e] Additionally adjusted for putative colorectal cancer risk factors in mid-adulthood: **BMI** (continuous), **menopausal status and menopausal hormone use** for NHS and NHSII only (premenopausal, postmenopausal never user, postmenopausal ever user, unknown menopausal status or hormone use), **family history of colorectal cancer** (yes, no), **personal history of diabetes** (yes, no), **pack-years of smoking** (continuous), **physical activity** (continuous), **regular use of aspirin** (yes, no), **regular use of nonsteroidal anti-inflammatory drugs** (yes, no), **current use of multivitamins** (yes, no), **intake of total calories, red and processed meat, dietary fiber, total folate [from foods and supplements] and total calcium** (all continuous), **Alternative Healthy Eating Index-2010 score without alcohol** (continuous) and **lower endoscopy due to screening** (yes, no) or **for other indications within the past 10 years** (yes, no).

Supplementary Table 3 Joint association of alcohol and cigarette use in early adulthood with risk of colorectal cancer

	Alcohol and cigarette use in early adulthood				
	<1 g/day of alcohol & <5 pack-years	1-<15 g/day of alcohol & <5 pack-years	≥15 g/day of alcohol & <5 pack-years	<15 g/day of alcohol & ≥5 pack-years	≥15 g/day of alcohol & ≥5 pack-years
Pooled					
Age-adjusted HR (95% CI)	1	1.06 (0.95 to 1.19)	1.59 (1.08 to 2.33)	1.27 (1.10 to 1.46)	1.38 (1.01 to 1.90)
Multivariable model 1 HR (95% CI)[a]	1	1.05 (0.93 to 1.17)	1.53 (1.04 to 2.24)	1.24 (1.08 to 1.43)	1.34 (0.97 to 1.84)
Multivariable model 2 HR (95% CI)[b]	1	1.02 (0.91 to 1.15)	1.45 (0.96 to 2.19)	1.20 (1.03 to 1.39)	1.22 (0.88 to 1.69)
Multivariable model 3 HR (95% CI)[c]	1	1.03 (0.92 to 1.16)	1.40 (0.95 to 2.06)	1.17 (1.04 to 1.32)	1.23 (0.87 to 1.73)
NHS					
Cases	410	377	5	460	5
Person-years	499,007	483,279	2,952	440,654	4,951
Age-adjusted HR (95% CI)	1	1.11 (0.97 to 1.28)	2.76 (1.13 to 6.70)	1.42 (1.24 to 1.62)	1.72 (0.71 to 4.18)
Multivariable model 1 HR (95% CI)[a]	1	1.10 (0.95 to 1.26)	2.64 (1.09 to 6.44)	1.37 (1.20 to 1.57)	1.58 (0.65 to 3.85)
Multivariable model 2 HR (95% CI)[b]	1	1.09 (0.94 to 1.26)	2.60 (1.07 to 6.34)	1.35 (1.18 to 1.55)	1.56 (0.64 to 3.80)
Multivariable model 3 HR (95% CI)[c]	1	1.09 (0.95 to 1.26)	2.39 (0.98 to 5.83)	1.20 (1.01 to 1.42)	1.31 (0.54 to 3.22)
NHSII					
Cases	147	93	7	91	7
Person-years	938,328	757,743	37,572	541,632	42,105
Age-adjusted HR (95% CI)	1	0.89 (0.68 to 1.15)	1.51 (0.70 to 3.24)	1.07 (0.82 to 1.39)	1.19 (0.56 to 2.55)
Multivariable model 1 HR (95% CI)[a]	1	0.87 (0.66 to 1.13)	1.40 (0.65 to 3.01)	1.03 (0.79 to 1.35)	1.10 (0.51 to 2.36)
Multivariable model 2 HR (95% CI)[b]	1	0.85 (0.65 to 1.12)	1.35 (0.63 to 2.94)	1.01 (0.77 to 1.33)	1.07 (0.49 to 2.31)
Multivariable model 3 HR (95% CI)[c]	1	0.86 (0.66 to 1.13)	1.40 (0.65 to 3.05)	0.92 (0.62 to 1.36)	1.00 (0.44 to 2.29)
HPFS					
Cases	307	208	16	461	30
Person-years	252,529	197,438	14,593	295,543	23,286
Age-adjusted HR (95% CI)	1	1.08 (0.90 to 1.30)	1.35 (0.81 to 2.26)	1.23 (1.06 to 1.42)	1.38 (0.94 to 2.02)
Multivariable model 1 HR (95% CI)[a]	1	1.07 (0.90 to 1.29)	1.32 (0.79 to 2.21)	1.23 (1.06 to 1.42)	1.36 (0.93 to 1.99)
Multivariable model 2 HR (95% CI)[b]	1	1.02 (0.85 to 1.23)	1.20 (0.72 to 2.01)	1.15 (0.99 to 1.34)	1.21 (0.82 to 1.78)
Multivariable model 3 HR (95% CI)[c]	1	1.04 (0.87 to 1.25)	1.17 (0.70 to 1.96)	1.20 (0.99 to 1.47)	1.27 (0.84 to 1.93)

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II

[a] Additionally adjusted for **race** (white, nonwhite), **height** (continuous), **BMI in early adulthood** (at age 18 for NHS and NHSII; at age 21 for HPFS [continuous]) and **physical activity at age 18-22** (in metabolic equivalent of task-hours/week for NHSII [continuous]; strenuous physical activity ≥2 times/week, 10-12 months/year for NHS and HPFS [yes, no]).

[b] Additionally adjusted for **cumulative alcohol intake in mid-adulthood** (continuous).

[c] Additionally adjusted for putative colorectal cancer risk factors in mid-adulthood: **BMI** (continuous), **menopausal status and menopausal hormone use** for NHS and NHSII only (premenopausal, postmenopausal never user, postmenopausal ever user, unknown menopausal status or hormone use), **family history of colorectal cancer** (yes, no**), personal history of diabetes** (yes, no), **pack-years of smoking** (continuous), **physical activity** (continuous), **regular use of aspirin** (yes, no), **regular use of nonsteroidal anti-inflammatory drugs** (yes, no), **current use of multivitamins** (yes, no), **intake of total calories, red and processed meat, dietary fiber, total folate [from foods and supplements] and total calcium** (all continuous), **Alternative Healthy Eating Index-2010 score without alcohol** (continuous) and **lower endoscopy due to screening** (yes, no) or **for other indications within the past 10 years** (yes, no).

Supplementary Table 4 Joint association of alcohol intake in early and mid-adulthood with risk of colorectal cancer

	Alcohol intake[a]				
	None in both life stages	Low in early adulthood & low in mid-adulthood	High in early adulthood & low in mid-adulthood	Low in early adulthood & high in mid-adulthood	High in early adulthood & high in mid-adulthood
Pooled					
Age-adjusted HR (95% CI)	1	1.10 (0.99 to 1.22)	1.50 (1.09 to 2.05)	1.34 (1.17 to 1.53)	1.46 (0.97 to 2.22)
Multivariable model 1 HR (95% CI)[b]	1	1.06 (0.96 to 1.18)	1.35 (0.98 to 1.86)	1.27 (1.11 to 1.46)	1.35 (0.89 to 2.05)
Multivariable model 2 HR (95% CI)[c]	1	1.11 (1.00 to 1.23)	1.39 (1.01 to 1.92)	1.32 (1.14 to 1.53)	1.39 (0.91 to 2.13)
NHS					
Cases	276	807	8	164	2
Person-years	333,772	935,244	6,556	153,924	1,347
Age-adjusted HR (95% CI)	1	1.17 (1.02 to 1.34)	1.95 (0.96 to 3.95)	1.35 (1.11 to 1.64)	2.87 (0.71 to 11.6)
Multivariable model 1 HR (95% CI)[b]	1	1.12 (0.97 to 1.28)	1.66 (0.81 to 3.38)	1.27 (1.04 to 1.55)	2.47 (0.61 to 10.1)
Multivariable model 2 HR (95% CI)[c]	1	1.15 (1.00 to 1.33)	1.58 (0.78 to 3.24)	1.30 (1.05 to 1.61)	2.51 (0.61 to 10.2)
NHSII					
Cases	102	210	13	19	1
Person-years	671,051	1,477,046	70,179	89,605	9,499
Age-adjusted HR (95% CI)	1	0.95 (0.74 to 1.20)	1.40 (0.78 to 2.51)	1.17 (0.72 to 1.92)	0.75 (0.10 to 5.41)
Multivariable model 1 HR (95% CI)[b]	1	0.91 (0.72 to 1.17)	1.24 (0.68 to 2.26)	1.12 (0.68 to 1.85)	0.69 (0.09 to 4.96)
Multivariable model 2 HR (95% CI)[c]	1	0.95 (0.74 to 1.21)	1.32 (0.73 to 2.41)	1.15 (0.69 to 1.94)	0.75 (0.10 to 5.49)
HPFS					
Cases	154	527	23	295	23
Person-years	126,891	432,025	20,480	186,593	17,399
Age-adjusted HR (95% CI)	1	1.10 (0.91 to 1.31)	1.40 (0.90 to 2.18)	1.35 (1.11 to 1.65)	1.41 (0.91 to 2.21)
Multivariable model 1 HR (95% CI)[b]	1	1.07 (0.89 to 1.29)	1.31 (0.83 to 2.05)	1.30 (1.06 to 1.59)	1.31 (0.84 to 2.06)
Multivariable model 2 HR (95% CI)[c]	1	1.13 (0.94 to 1.36)	1.36 (0.87 to 2.14)	1.38 (1.11 to 1.71)	1.35 (0.86 to 2.14)

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II

[a] Alcohol intake of none was defined as <1 g/day, low as <15 g/day and high as ≥15 g/day.

[b] Additionally adjusted for **race** (white, nonwhite), **height** (continuous), **BMI in early adulthood** (at age 18 for NHS and NHSII; at age 21 for HPFS [continuous]), **pack-years of smoking before age 30** (continuous) and **physical activity at age 18-22** (in metabolic equivalent of task-hours/week for NHSII [continuous]; strenuous physical activity ≥2 times/week, 10-12 months/year for NHS and HPFS [yes, no]).

[c] Additionally adjusted for putative colorectal cancer risk factors in mid-adulthood: **BMI** (continuous), **menopausal status and menopausal hormone use** for NHS and NHSII only (premenopausal, postmenopausal never user, postmenopausal ever user, unknown menopausal status or hormone use), **family history of colorectal cancer** (yes, no), **personal history of diabetes** (yes, no), **pack-years of smoking** (continuous), **physical activity** (continuous), **regular use of aspirin** (yes, no), **regular use of nonsteroidal anti-inflammatory drugs** (yes, no)**, current use of multivitamins** (yes, no), **intake of total calories, red and processed meat, dietary fiber, total folate [from foods and supplements] and total calcium** (all continuous), **Alternative Healthy Eating Index-2010 score without alcohol** (continuous) and **lower endoscopy due to screening** (yes, no) or **for other indications within the past 10 years** (yes, no).