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No association between garlic intake and risk of colorectal cancer

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Abstract

Background—Although experimental studies suggested beneficial role of garlic intake on colorectal carcinogenesis, limited prospective cohort studies have evaluated garlic intake in relation to colorectal cancer (CRC) incidence.

Methods—We followed 76,208 women in the Nurses' Health Study and 45,592 men in the Health Professionals Follow-up Study for up to 24 years and examined garlic intake and garlic supplement use in relation to CRC risk. Information on garlic intake and supplement use was assessed using a validated food frequency questionnaire and a Cox proportional hazard regression model was used to estimate the multivariable hazard ratio (MV-HR) and 95% confidence intervals (95% CIs).

Results—We documented 2,368 (1,339 women and 1,029 men) incident CRC cases and found no association between garlic intake and CRC risk; the MV-HRs (95% CIs) associated with garlic (1 clove or 4 shakes per serving) intake 1/day compared with <1/month were 1.21 (0.94–1.57; p-trend=0.14) for women and 1.00 (0.71–1.42; p-trend=0.89) for men. The MV-HRs (95% CIs) of

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No potential conflicts of interest were disclosed.

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CRC for garlic supplement use, which was used in 6% of the participants in each study, were 0.72 (0.48–1.07) for women and 1.22 (0.83–1.78) for men.

Conclusion—Our prospective data do not support an important role of garlic intake or garlic supplement use in colorectal carcinogenesis.

Keywords

Garlic intake; colorectal cancer; incidence; prospective study; garlic supplement; carcinogenesis

Introduction

Many experimental studies have demonstrated the potential mechanisms for the beneficial effect of garlic on colorectal cancer (CRC). An expert review panel organized by World Cancer Research Fund and American Institute for Cancer Research concluded garlic intake as a “probable” protective factor against colorectal cancer (CRC)¹. However, epidemiologic evidence on garlic intake or garlic supplement use and CRC risk is limited². We prospectively evaluated the association between garlic intake and garlic supplement use and CRC risk in two cohorts of women (the Nurses’ Health Study, NHS) and men (the Health Professionals Follow-up Study, HPFS).

Material and Methods

The NHS and HPFS have been described elsewhere^{3, 4}. Briefly, the NHS included 121,700 female registered nurses who were 30 to 55 years of age in 1976 while the HPFS consists of 51,529 male health professionals aged 40 to 75 years in 1986. Participants have been sent questionnaires every 2 years to collect information on lifestyle factors and disease endpoints. Both studies have been approved by the institutional review board at the Brigham and Women’s Hospital and the Harvard School of Public Health, Boston, Massachusetts. Return of the questionnaires was considered to imply informed consent.

A semiquantitative food frequency questionnaire (FFQ) with ~130 foods including information on daily garlic intake (1 clove or 4 shakes per serving) was sent to the study participants in 1984, 1994, 1998, 2002, 2006 and 2008 in NHS and in 1986, 1994, 1998, 2002, 2006 and 2008 in HPFS. The questionnaire had nine possible responses for garlic intake frequency, ranging from never or less than one serving per month to six or more servings per week. Participants also responded to the question: “Are there other supplements that you take on a regular basis?” with garlic supplements as one of the options (yes, no) in 1998 and 2002 in NHS and biennially from 1996 to 2006 in HPFS. We calculated a cumulative garlic intake to better represent the long-term intake. We treated 1984 as baseline in NHS and 1986 as baseline in HPFS when garlic intake was first measured. We excluded participants with an implausible caloric intake or those who had reported a diagnosis of cancer (except nonmelanoma skin cancer) or ulcerative colitis at baseline.

Biennial follow-up questionnaires were used to identify newly diagnosed cases of CRC. Information on anatomic location, stage, and histological type of the cancer was also collected. Deaths were documented by responses to follow-up questionnaires by family members or the postal service and by a search of the National Death Index. Participants contributed person-time from the date of returning the questionnaire till the date of any type of CRC diagnosis, death, or June 2008 for NHS or Jan 2008 for HPFS, whichever came first. Hazard Ratio (HR) of CRC (and 95% confidence interval) in relation to garlic intake or garlic supplement use were calculated using Cox proportional hazards regression models after adjusting for potential confounding factors (see footnotes in Table 2 for categorizations).

Results

During 24 years of follow-up among 76,208 women in the NHS and 22 years among 45,592 men in the HPFS, we documented 2,387 cases of invasive CRC (1,339 women and 1,029 men). Participants with higher garlic intake tended to be physically active, past smokers, and have higher intakes of alcohol, calcium, vitamin D, and folate (Table 1). Cumulative garlic intake was not inversely associated with risk of either CRC or any sub-site of CRC (Table 2). Age-adjusted results were essentially similar to the multivariable-adjusted results. Null associations were observed when we examined the baseline garlic intake (data not shown). In 1998, 6% of the participants used garlic supplements in both cohorts. Use of garlic supplement was not associated with CRC risk (Supplementary Table 1).

Discussion

Garlic (*Allium sativum*) has medical effects. The major compounds responsible for its health benefits are sulfur-containing compounds⁵. Both *in vitro* and *in vivo* studies showed that garlic and its compounds exert protective effect on colonic carcinogenesis by inhibiting carcinogen-induced DNA adduct formation, cell proliferation, and angiogenesis, inducing antitumorigenic genes and apoptosis, and redistributing cell cycle growth phases^{2, 6, 7}. Despite the experimental evidence, epidemiological data are limited and inconclusive. Four prospective cohort studies have reported on garlic consumption and the risk of CRC. A systemic review of garlic intake and CRC in 2007 reported that four (1 cohort and 3 case-control) studies out of 7 (3 cohort and 4 case control studies) suggested a protective effect². The four studies showing protective effect were conducted in China, Switzerland, Argentina, and US in the 1990's and adjusted for limited number of confounders. Among them, a cohort study of postmenopausal women, which used a similar FFQ as our study, found an inverse association for garlic intake of 1 serving/wk⁸ (HR=0.65, 95% CI: 0.44–0.97). In 2006, a case-control study utilizing data from an integrated network of Italian and Swiss case-control studies found an inverse association between garlic intake and CRC risk (OR=0.74, 95% CI: 0.63, 0.86).⁹ The latest study by McCullough et. al. using the Cancer Prevention Study II Nutrition Cohort reported a HR of 1.04 (0.99–1.08) in men for each serving/wk of garlic, and 0.95 (0.91–1.00) in women¹⁰. In our study, we found no association for garlic intake of up to 1 serving/d. The strengths of our study include large sample size, relatively wide variation in garlic intake, and measurement of many risk factors for CRC. Because garlic supplement use was low in our populations, we had a limited power to detect an association. Also, we did not have information on dose or type of the supplement used by the participants. In conclusion, we found null associations between intakes of garlic or use of garlic supplements and CRC risk. Further research in other populations with high use of garlic supplements is needed. Studies using biomarkers that reflect the actual active garlic component in human body may be desired as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CRC	colorectal cancer
MV-HR	multivariable hazard ratio
95% CIs	95% confidence intervals
NHS	the Nurses' Health Study
HPFS	the Health Professionals Follow-up Study
FFQ	food frequency questionnaire

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Table 1

Age-standardized characteristics by garlic intake in the Nurses' Health Study (NHS; in 1984) and in the Health Professionals Follow-up Study (HPFS; in 1986)

Characteristics	Frequency of garlic intake (1 clove or 4 shakes)-NHS					Frequency of garlic intake (1 clove or 4 shakes)-HPFS						
	<1/month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	<1/month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day
Total number	24485	17196	14846	11721	4081	3879	20913	9890	6284	5448	1685	1372
Age, mean (SD), y	52(7)	51(7)	50(7)	51(7)	51(7)	51(7)	54(10)	54(10)	53(9)	54(9)	54(9)	54(9)
Body Mass Index (kg/m ²), mean (SD)*	25.1(4.8)	24.8(4.5)	24.9(4.6)	25.1(4.8)	25.4(5.0)	25.6(5.2)	25.4(3.1)	25.6(3.2)	25.6(3.2)	25.6(3.4)	25.8(3.2)	25.9(3.6)
Physical Activity (MET-hrs/wk), mean(SD)**	14.8(21.6)	14.8(20.1)	15.2(20.9)	16.3(22.5)	17.5(21.7)	18.4(25.0)	27.7(31.4)	28.2(33.2)	29.8(34.8)	30.2(34.1)	30.8(40.4)	33.1(37.0)
History of colorectal cancer in a parent or sibling (%)	8	8	8	8	9	8	8	8	8	9	9	9
Past smokers (%)	34	37	40	42	43	43	39	44	46	47	50	50
Current smokers (%)	15	17	18	18	17	15	8	9	9	9	8	8
Regular aspirin use (%) †	40	39	39	40	39	39	29	29	29	29	29	31
Ever postmenopausal hormone use (%)	45	46	45	46	46	46	NA					
Dietary intake, mean (SD)												
Alcohol consumption (g/d)	4.8(9.2)	6.7(10.8)	7.7(11.6)	9.0(12.9)	9.1(12.7)	9.1(13.4)	9.2(13.9)	12.1(15.7)	13.2(15.8)	14.4(17.0)	16.1(18.5)	14.9(18.8)
Total calcium intake (mg/d) ‡	873(433)	879(431)	878(422)	888(420)	921(451)	915(440)	904(423)	885(420)	889(417)	896(434)	885(429)	931(455)
Total vitamin D intake (IU/d) ‡	309(249)	312(243)	310(240)	319(248)	326(252)	335(267)	395(297)	403(309)	416(331)	418(320)	435(337)	471(371)
Total folate intake (ug/d) ‡	370(232)	376(224)	380(226)	397(233)	415(236)	447(256)	463(265)	472(274)	489(280)	504(283)	533(296)	583(340)
Beef, pork, or lamb as a main dish (servings/wk)	2.3(1.5)	2.3(1.5)	2.3(1.5)	2.4(1.5)	2.4(1.6)	2.4(1.7)	1.8(1.7)	1.8(1.6)	1.7(1.5)	1.8(1.6)	1.7(1.6)	1.7(1.9)
Processed meat intake (servings/wk)	1.0(1.4)	1.1(1.3)	1.1(1.4)	1.1(1.4)	1.1(1.3)	1.1(1.6)	1.2(1.9)	1.3(1.9)	1.2(1.7)	1.2(1.7)	1.2(2.0)	1.0(1.8)

* Body mass index was calculated as weight in kilograms divided by the square of height in meters.

** MET denotes metabolic equivalent. MET-hours = sum of the average time/week spent in each activity × MET value of each activity.

† Regular aspirin user was defined as consumption of 2 or more 325-mg tablets per week. Non-regular user was defined otherwise.

‡ Nutrient values were energy-adjusted intake.

Table 2
 Cumulative Garlic Intake & Colorectal Cancer Risk in the Nurses' Health Study (NHS; 1984–2008) and Health Professionals Follow-up Study (HPFS; 1986–2008)

		Frequency of garlic intake (1 clove or 4 shakes)					P for trend	
		<1/month	1–3 per month	1 per week	2–4 per week	5–6 per week		
<i>NHS</i>								
<i>Colorectal cancer</i>	<i>No of Cases-1339</i>	<u>283</u>	<u>296</u>	<u>227</u>	<u>327</u>	<u>128</u>	<u>78</u>	
	Model 1 *	1.0 (ref.)	1.11 (0.94,1.30)	1.07 (0.90,1.28)	1.22 (1.04,1.44)	1.19 (0.96,1.47)	1.20 (0.93,1.54)	0.14
	Model 2 ***	1.0 (ref.)	1.12 (0.95,1.32)	1.08 (0.90,1.28)	1.25 (1.06,1.47)	1.21 (0.98,1.50)	1.22 (0.95,1.57)	0.11
	Model 3 †	1.0 (ref.)	1.11 (0.94,1.31)	1.07 (0.89,1.27)	1.23 (1.04,1.45)	1.20 (0.96,1.48)	1.21 (0.94,1.57)	0.14
<i>Colon cancer</i>	<i>No of Cases-1054</i>	<u>222</u>	<u>236</u>	<u>177</u>	<u>252</u>	<u>104</u>	<u>63</u>	
	Model 1 *	1.0 (ref.)	1.11 (0.93,1.34)	1.06 (0.87,1.30)	1.19 (0.99,1.43)	1.22 (0.96,1.55)	1.23 (0.93,1.63)	0.13
	Model 2 ***	1.0 (ref.)	1.13 (0.94,1.36)	1.06 (0.87,1.30)	1.21 (1.00,1.46)	1.23 (0.97,1.56)	1.25 (0.94,1.65)	0.11
	Model 3 †	1.0 (ref.)	1.12 (0.93,1.34)	1.05 (0.86,1.28)	1.19 (0.98,1.43)	1.21 (0.95,1.53)	1.23 (0.92,1.64)	0.15
<i>Proximal colon cancer</i>	<i>No of Cases-634</i>	<u>136</u>	<u>140</u>	<u>95</u>	<u>162</u>	<u>64</u>	<u>37</u>	
	Model 1 *	1.0 (ref.)	1.05 (0.83,1.33)	0.93 (0.71,1.21)	1.20 (0.95,1.52)	1.18 (0.87,1.59)	1.15 (0.80,1.66)	0.26
	Model 2 ***	1.0 (ref.)	1.05 (0.82,1.33)	0.91 (0.70,1.19)	1.19 (0.94,1.50)	1.15 (0.85,1.56)	1.13 (0.79,1.64)	0.31
	Model 3 †	1.0 (ref.)	1.03 (0.81,1.31)	0.90 (0.69,1.18)	1.17 (0.92,1.48)	1.13 (0.83,1.53)	1.13 (0.78,1.64)	0.33
<i>Distal colon cancer</i>	<i>No of Cases-397</i>	<u>82</u>	<u>93</u>	<u>75</u>	<u>85</u>	<u>37</u>	<u>25</u>	
	Model 1 *	1.0 (ref.)	1.23 (0.91,1.66)	1.23 (0.89,1.69)	1.17 (0.86,1.59)	1.25 (0.84,1.86)	1.36 (0.87,2.14)	0.33
	Model 2 ***	1.0 (ref.)	1.28 (0.94,1.72)	1.25 (0.91,1.71)	1.22 (0.89,1.67)	1.31 (0.88,1.95)	1.43 (0.91,2.26)	0.23
	Model 3 †	1.0 (ref.)	1.27 (0.94,1.71)	1.22 (0.88,1.68)	1.19 (0.87,1.63)	1.28 (0.85,1.91)	1.39 (0.88,2.20)	0.30
<i>Rectal cancer</i>	<i>No of Cases-285</i>	<u>61</u>	<u>60</u>	<u>50</u>	<u>75</u>	<u>24</u>	<u>15</u>	
	Model 1 *	1.0 (ref.)	1.08 (0.75,1.55)	1.12 (0.77,1.64)	1.34 (0.95,1.90)	1.09 (0.67,1.76)	1.09 (0.62,1.92)	0.78
	Model 2 ***	1.0 (ref.)	1.09 (0.76,1.57)	1.14 (0.78,1.67)	1.40 (0.99,1.99)	1.14 (0.70,1.85)	1.12 (0.63,1.99)	0.65
	Model 3 †	1.0 (ref.)	1.09 (0.76,1.57)	1.13 (0.77,1.66)	1.40 (0.98,2.00)	1.14 (0.70,1.86)	1.14 (0.64,2.03)	0.68
<i>HPFS</i>								
<i>Colorectal cancer</i>	<i>No of Cases-1029</i>	<u>400</u>	<u>248</u>	<u>127</u>	<u>163</u>	<u>56</u>	<u>35</u>	
	Model 1 *	1.0 (ref.)	0.99 (0.84,1.16)	0.95 (0.78,1.16)	0.97 (0.80,1.17)	0.92 (0.69,1.22)	1.03 (0.73,1.45)	0.99

		Frequency of garlic intake (1 clove or 4 shakes)						
		<1/month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	P for trend
Model2**		1.0 (ref.)	1.00 (0.85,1.17)	0.95 (0.78,1.17)	0.98 (0.81,1.19)	0.92 (0.69,1.22)	1.01 (0.72,1.42)	0.91
Model3†		1.0 (ref.)	0.99 (0.84,1.16)	0.93 (0.76,1.14)	0.96 (0.80,1.17)	0.90 (0.67,1.20)	1.00 (0.71,1.42)	0.89
Colon cancer	No. of Cases-811	323	194	97	126	40	31	
Model1*		1.0 (ref.)	0.96 (0.80,1.15)	0.92 (0.73,1.15)	0.94 (0.76,1.17)	0.82 (0.58,1.14)	1.15 (0.80,1.65)	0.70
Model2**		1.0 (ref.)	0.97 (0.81,1.17)	0.92 (0.73,1.16)	0.96 (0.78,1.19)	0.81 (0.58,1.13)	1.12 (0.78,1.62)	0.77
Model3†		1.0 (ref.)	0.96 (0.80,1.15)	0.90 (0.70,1.13)	0.93 (0.75,1.16)	0.78 (0.55,1.09)	1.09 (0.76,1.58)	0.90
Proximal colon cancer	No. of Cases-345	134	78	44	59	14	16	
Model1*		1.0 (ref.)	0.92 (0.69,1.22)	1.02 (0.72,1.44)	1.05 (0.77,1.43)	0.66 (0.38,1.15)	1.42 (0.85,2.37)	0.31
Model2**		1.0 (ref.)	0.92 (0.69,1.23)	1.01 (0.71,1.43)	1.04 (0.76,1.43)	0.65 (0.37,1.13)	1.39 (0.83,2.32)	0.37
Model3†		1.0 (ref.)	0.92 (0.69,1.23)	1.00 (0.70,1.41)	1.04 (0.75,1.43)	0.63 (0.36,1.11)	1.35 (0.80,2.28)	0.43
Distal colon cancer	No. of Cases-314	131	76	33	43	20	11	
Model1*		1.0 (ref.)	0.98 (0.74,1.31)	0.74 (0.50,1.10)	0.84 (0.59,1.19)	1.10 (0.68,1.78)	1.03 (0.56,1.86)	0.87
Model2**		1.0 (ref.)	0.99 (0.74,1.32)	0.75 (0.51,1.11)	0.86 (0.60,1.22)	1.10 (0.68,1.78)	1.03 (0.56,1.87)	0.85
Model3†		1.0 (ref.)	0.97 (0.72,1.30)	0.73 (0.49,1.08)	0.82 (0.57,1.17)	1.05 (0.64,1.71)	1.01 (0.55,1.86)	0.91
Rectal cancer	No. of Cases-218	77	54	30	37	16	4	
Model1*		1.0 (ref.)	1.09 (0.76,1.55)	1.09 (0.71,1.67)	1.08 (0.72,1.61)	1.33 (0.76,2.30)	0.56 (0.20,1.54)	0.44
Model2**		1.0 (ref.)	1.10 (0.77,1.57)	1.09 (0.71,1.68)	1.08 (0.72,1.62)	1.37 (0.79,2.39)	0.55 (0.20,1.52)	0.44
Model3†		1.0 (ref.)	1.10 (0.77,1.57)	1.10 (0.72,1.70)	1.10 (0.73,1.65)	1.45 (0.82,2.54)	0.60 (0.22,1.66)	0.56

* Model1 was adjusted for age (in months)

** Model2 was adjusted for age (in months), body mass index (<25, 25-30, 30 kg/m²), smoking before age 30 (0, 1-4, 5-10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes, no), history of endoscopy screening (yes, no), regular aspirin use (yes, no), physical activity (< 3, 3-27, 27 MET-hrs/wk), and postmenopausal hormone use (premenopausal, never, past, or current user).

† Model3 was further adjusted for beef, pork, and lamb as a main dish (quintiles), consumption of processed meat (quintiles), alcohol consumption (0-<5, 5-<10, 10-<15, or 15 g/d), energy-adjusted total calcium intake (quintiles), total folate (quintiles), total vitamin D intake (quintiles), and total energy intake (quintiles).