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Associations of red and processed meat with survival after colorectal cancer and differences according to timing of dietary assessment[1,2]

*Prudence R Carr,[3] Lina Jansen,[3] Viola Walter,[3] Matthias Kloor,[8] Wilfried Roth,[6,9] Hendrik Bläker,[10] Jenny Chang-Claude,[4] Hermann Brenner,[3,5,7] and Michael Hoffmeister[3]**

Divisions of [3]Clinical Epidemiology and Aging Research, [4]Cancer Epidemiology, and [5]Preventive Oncology; [6]Unit of Molecular Tumor Pathology; and [7]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany; Departments of [8]Applied Tumor Biology and [9]Pathology, Institute of Pathology, University of Heidelberg, Heidelberg, Germany; and [10]Institute of Pathology, Charité University Medicine, Berlin, Germany

ABSTRACT

Background: Little is known about the prognostic impact of red and processed meat intake or about changes in consumption after a diagnosis of colorectal cancer (CRC).

Objectives: We investigated associations of baseline red and processed meat with survival outcomes and explored changes in intake among CRC survivors 5 y after diagnosis.

Design: A total of 3122 patients diagnosed with CRC between 2003 and 2010 were followed for a median of 4.8 y [DACHS (Darmkrebs: Chancen der Verhütung durch Screening) study]. Patients provided information on diet and other factors in standardized questionnaires at baseline and at the 5-y follow-up. Cox proportional hazards regression models were used to estimate HRs and 95% CIs.

Results: Among patients with stage I–III CRC, baseline red and processed meat intake was not associated with overall (>1 time/d compared with <1 time/d; HR: 0.85; 95% CI: 0.67, 1.09), CRC-specific (HR: 0.83; 95% CI: 0.61, 1.14), cardiovascular disease–specific (HR: 0.92; 95% CI: 0.51, 1.68), non–CRC-specific (HR: 0.88; 95% CI: 0.59, 1.30), and recurrence-free (HR: 1.03; 95% CI: 0.80, 1.33) survival; results among stage IV patients were comparable. An association with worse overall survival was found among patients with Kirsten rat sarcoma viral oncogene homolog (*KRAS*)-mutated CRC (HR: 1.99; 95% CI: 1.10, 3.56) but not with microsatellite instability or CpG island methylator phenotype (CIMP) positivity. A much lower proportion of survivors reported daily consumption of red and processed meat at the 5-y follow-up than at baseline (concordance rate: 39%; κ-value: 0.10; 95% CI: 0.07, 0.13).

Conclusions: Our findings suggest that baseline red and processed meat intake is not associated with poorer survival among patients with CRC. The potential interaction with *KRAS* mutation status warrants further evaluation. Major changes in consumption measured at the 5-y follow-up may have had an impact on our survival estimates. *Am J Clin Nutr* 2016;103:192–200.

Keywords: colorectal cancer, molecular subtypes, mortality, red and processed meat, survival

INTRODUCTION

In 2011, the World Cancer Research Fund/American Institute for Cancer Research report judged the evidence for red and processed meat as a risk factor for colorectal cancer (CRC)[11] to be convincing (1). In contrast, the evidence for its role in CRC survival is limited (2, 3).

Few studies have investigated the association between meat consumption and CRC outcomes (4–7), and only one study specifically examined red and processed meat intake and CRC survival (5). Red and processed meat intake before CRC diagnosis was associated with a higher risk of all-cause mortality (highest compared with lowest quartile; RR: 1.29; 95% CI: 1.05, 1.59) and cardiovascular disease (CVD)–specific death (RR: 1.63; 95% CI: 1.00, 2.67) but not CRC-specific death (RR: 1.09; 95% CI: 0.79, 1.51) (5). No associations were found with postdiagnostic red and processed meat intake. Two other studies that assessed the associations between prediagnostic meat intake (not limited to red and processed meat) and CRC survival did not show any associations (4, 7).

Previous studies (8–13) have reported that cancer survivors make dietary modifications after their cancer diagnosis to improve overall health. However, most of these studies were conducted in patients with breast cancer and currently little evidence is available for CRC survivors with regard to the role of dietary factors (2, 3, 14–17). Moreover, adverse effects from surgery or adjuvant treatment may also affect patients' dietary habits after a CRC diagnosis, and therefore the timing of the dietary assessment may play a role. Thus, the aims of this study

[1] Supported by the German Research Council (BR 1704/6-1, BR 1704/6-3, BR 1704/6-4, CH 117/1-1, and HO 5117/2-1), the German Federal Ministry of Education and Research (01KH0404 and 01ER0814), and the Interdisciplinary Research Program of the National Center for Tumor Diseases, Germany.

[2] Supplemental Tables 1–6 and Supplemental Figure 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

*To whom correspondence should be addressed. E-mail m.hoffmeister@dkfz.de.

[11] Abbreviations used: CIMP, CpG island methylator phenotype; CRC, colorectal cancer; CVD, cardiovascular disease; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; FFQ, food-frequency questionnaire; ICD-10, International Classification of Diseases, 10th Revision; KRAS, Kirsten rat sarcoma viral oncogene homolog.

Received August 11, 2015. Accepted for publication October 7, 2015.

First published online November 25, 2015; doi: 10.3945/ajcn.115.121145.

were to investigate prediagnostic red and processed meat intake and its association with survival of patients with CRC overall and according to the timing of patient recruitment and to explore dietary changes in red and processed meat intake among survivors 5 y after diagnosis in a large population-based setting in Germany.

METHODS

Study design and study population

The DACHS (Darmkrebs: Chancen der Verhütung durch Screening) study is an ongoing population-based case-control study in the Rhine-Neckar region in southwest Germany. Patients with a histologically confirmed first diagnosis of CRC [International Classification of Diseases, 10th Revision (ICD-10), codes C18–C20] are eligible to participate if they can speak German, are at least 30 y of age, and are physically able to participate in an interview lasting ~1 h. Further details of the DACHS study were reported elsewhere (18–21). Patients diagnosed with CRC between 2003 and 2010 were included in this analysis. The DACHS study was approved by the ethics committees of the University of Heidelberg and the state medical boards of Baden-Württemberg and Rhineland-Palatinate. Written informed consent was given by all participants.

Data collection and follow-up

At baseline, patients participated in an interview with trained interviewers who collected information on patients' sociodemographic, medical, and lifestyle history by using a standardized questionnaire. Eligible participants were informed about the study, usually a few days after surgery. Patients who could not be recruited during their hospital stay were contacted after discharge by clinicians or by clinical cancer registries. The median time between diagnosis and interview was 24 d (IQR: 10–224 d). The vital status of participants was determined through population registries at 3 and 5 y after CRC diagnosis. Information about CRC treatment and recurrence was collected from the patients' attending physicians ~3 y after diagnosis by using a standardized questionnaire. Approximately 5 y after diagnosis, patients completed a standardized follow-up questionnaire on medical, lifestyle, and recurrence history. New diagnoses and cancer recurrences were verified through medical records. In cases in which the patient died before follow-up or did not complete the follow-up questionnaire, information on cancer recurrence before death was collected from the last attending physicians. Death certificates were obtained from health authorities to verify causes of death.

Dietary assessment

Prediagnostic diet was assessed at baseline by using a 23-item food-frequency questionnaire (FFQ). Participants were asked to report their average frequency of consumption over the previous 12 mo before diagnosis from 6 possible responses ("never" to "more than once per day"). The FFQ did not assess portion sizes. Red meat included fresh pork, beef, lamb, and sausages made from beef or pork. Processed meat included processed lunch meat, ham, and salami. If information on any of the meat items was missing, the participants were excluded (n = 11). The postdiagnostic diet of CRC survivors was assessed by using a similar FFQ at the 5-y follow-up. Three groups of red and processed meat intake (>1 time/d, 1 time/d, and <1 time/d) were created for analyses by summing the frequency of consumption of red meat and of processed meat (**Supplemental Table 1**).

Tumor tissue analyses

Tumor tissue analyses were available for a subsample of patients (n = 1245). For the determination of high level microsatellite instability, a mononucleotide marker panel (BAT25, BAT26, and CAT25) was used in sections of the tumor block (22). For the presence of *KRAS* mutations we used a single-stranded conformational polymorphism technique (23) and analyzed the CpG island methylator phenotype (CIMP) after DNA bisulfite conversion as previously described (18, 24).

Statistical analyses

The distributions of baseline characteristics of all included patients and of CRC survivors at the 5-y follow-up were compared by using chi-square tests. Likewise, we compared the distribution of patient characteristics by groups of baseline red and processed meat intake. Because the time interval between diagnosis and baseline interview varied for patients, we assessed differences in red and processed meat intakes collected at different time periods after diagnosis (i.e., <1 compared with ≥1 to ≤6 compared with >6 mo postdiagnosis). In addition, for those patients who received chemotherapy (stage II–IV patients), we assessed differences in dietary information collected at different time periods depending on whether the patient was receiving treatment (i.e., interview before surgery, interview after surgery but before the start of chemotherapy, interview between the start of chemotherapy and end of chemotherapy, and interview after chemotherapy ended). We calculated ordinal polytomous logistic regression models for the odds of consuming higher amounts (from low to high: <1 time/d, 1 time/d, >1 time/d) of red and processed meat depending on the timing of the FFQ using different levels of adjustment. Furthermore, we assessed postdiagnostic consistency of red and processed meat intake using Cohen's κ coefficient by comparing red and processed meat intake reported at baseline and at the 5-y follow-up among CRC survivors.

Cox proportional hazards regression models were used to calculate HRs and 95% CIs for the association of baseline red and processed meat intake (>1 time/d or 1 time/d compared with <1 time/d or per increase in group) with overall, CRC-specific (ICD-10 codes C18–C20), CVD-specific (ICD-10 codes I00–I99), non–CRC-specific (causes of death other than CRC), and recurrence-free survival (recurrence or death from CRC).

We decided a priori to separate results for patients with stage I–III and stage IV CRC because the overall survival rate for stage IV patients is relatively poor. Patients who did not have an endpoint of interest were censored at the last contact they were known to be alive or free of recurrence, respectively. Median follow-up time was calculated by using the Kaplan-Meier estimate of potential follow-up (25). All survival analyses were adjusted for late entry into the study because most patients were interviewed at various time intervals after CRC diagnosis. To

test the proportional hazards assumption, we calculated Schoenfeld residuals and examined the effect of including time-dependent components for each explanatory variable in the Cox model. We included age at diagnosis, sex, and tumor stage at diagnosis in all Cox models. Following a forward-selection approach ($P < 0.10$), models also included adjustment for chemotherapy, surgery, BMI, physical activity, history of diabetes, stroke, heart failure, myocardial infarction, dairy intake, whole-grain intake, time between diagnosis and interview, and for a time-dependent effect of chemotherapy [chemotherapy × log(time)].

We repeated the analyses of overall and CRC-specific survival stratified by age, sex, cancer site, tumor stage, family history of CRC, BMI, and on the timing of the baseline assessment. Analyses of overall survival were repeated according to molecular tumor subtype. For consistency with the one previous study on the association of red and processed meat and survival after CRC (5), we repeated the analyses on prediagnostic red and processed meat intake adjusted by the same covariates as used in their Cox models.

Multiple imputation with the use of the Markov-chain Monte Carlo method was performed to fill in missing data for covariates (n = 10 imputed data sets; SAS procedure PROC MI) (26). All of the analyses were performed by using SAS version 9.3 (SAS Institute). Statistical tests were 2-sided, with an α level of 0.05.

RESULTS

Of the 3146 patients diagnosed with CRC, we excluded patients with missing information on meat items (n = 11), follow-up time (n = 3), and cancer stage (n = 10). **Table 1** shows the distribution of clinical, sociodemographic, and other characteristics at baseline (n = 3122) according to red and processed meat intake and overall baseline characteristics among the subset of participants who survived and who completed the 5-y follow-up questionnaire (n = 864). (See **Supplemental Figure 1** for patients included in the analyses.)

Participants were, on average, 68 y old at CRC diagnosis. More-frequent meat eaters were younger, more likely to be male, overweight or obese, less physically active, more likely to smoke and drink more alcohol, more likely to have a lower intake of dairy foods and whole grains, and more likely to report a history of hypertension (Table 1). Compared with all patients, patients who also completed the 5-y follow-up questionnaire (net response rate: 86%) were younger at cancer diagnosis (mean age at diagnosis: 65.9 y), more often had a lower cancer stage, received chemotherapy less often, drank less alcohol, ate whole grains more often, and less often had a history of diabetes, stroke, or heart failure (Table 1).

Among the 3122 patients included in the analyses, a total of 864 deaths occurred, of which 630 were deaths from CRC and 102 were deaths from CVD; 900 patients had a recurrence. Median follow-up time was 4.8 y (25th percentile: 2.9 y; 75th percentile: 5.0 y).

In multivariate analyses, prediagnostic red and processed meat intake was not associated with overall (>1 time/d compared with <1 time/d; HR: 0.85; 95% CI: 0.67, 1.09), CRC-specific (HR: 0.83; 95% CI: 0.61, 1.14), CVD-specific (HR: 0.92; 95% CI: 0.51, 1.68), non–CRC-specific (HR: 0.88; 95% CI: 0.59,1.30), or recurrence-free (HR: 1.03; 95% CI: 0.80, 1.33) survival in patients with stage I–III CRC (**Table 2**). We did not find any association for red meat or for processed meat when analyzed separately (**Supplemental Tables 2** and **3**), and results for stage IV patients were comparable (**Supplemental Table 4**).

No associations were found between prediagnostic red and processed meat intake and overall or CRC-specific survival stratified by age, sex, BMI, or family history of CRC (**Supplemental Table 5**). However, we observed a significant association with better overall survival for cancers of the rectum among those in the highest group of red and processed meat intake (HR: 0.63; 95% CI: 0.43, 0.93). Red and processed meat consumption in the highest category compared with the lowest was associated with improved survival among those who completed the questionnaire within 1 mo of CRC diagnosis (HR: 0.66; 95% CI: 0.47, 0.92) and among those who completed the questionnaire between surgery and the start of chemotherapy (HR: 0.46; 95% CI: 0.23, 0.89). Stratification by stage at diagnosis showed that a higher intake of red and processed meat was significantly associated with CRC-specific survival (HR: 0.54; 95% CI: 0.30, 0.96) for patients with stage I–II CRC, but no associations were seen with overall survival (Supplemental Table 5).

Analyses stratified by molecular pathologic subtypes of CRC indicated a significant association only with overall survival for *KRAS*-mutated CRC (HR: 1.99; 95% CI: 1.10, 3.56; P-interaction = 0.09) when comparing the highest with the lowest intake of red and processed meat. No effect modifications were observed (**Table 3**). In sensitivity analyses, results were adjusted for the same covariates as used in the study by McCullough et al. (5) did not show any associations when comparing the highest with the lowest intake of red and processed meat and overall, CRC-specific, or CVD-specific survival (**Supplemental Table 6**).

After adjustment for age, sex, and cancer stage, patients who completed the questionnaire >6 mo after diagnosis (OR: 1.30; 95% CI: 1.11, 1.54) or between 1 and 6 mo after diagnosis (OR: 1.28; 95% CI: 1.06, 1.56) were more likely to report higher amounts of red and processed meat consumption than those who completed the questionnaire within 1 mo of diagnosis (**Table 4**). Furthermore, patients who completed the FFQ while they were undergoing chemotherapy (OR: 1.73; 95% CI: 1.22, 2.46) were more likely to report higher intakes of red and processed meat than those patients who completed the FFQ after surgery but before the start of chemotherapy (Table 4).

Of the 3122 patients included in the baseline analysis, 864 completed the 5-y follow-up FFQ (**Table 5**). There was a dramatic decrease in the proportion of patients who consumed red and processed meat >1 time/d (from 28.7% to 2.9%) or 1 time/d (from 37.4% to 14.5%), with only slight agreement between red and processed meat intake reported at baseline and red and processed meat intake reported at the 5-y follow-up among CRC survivors (Cohen's κ value = 0.10; 95% CI: 0.07, 0.13).

DISCUSSION

In this large population-based study in 3122 patients with CRC, we found no significant association between prediagnostic red and processed meat intake and overall, CRC-specific, CVD-specific, non–CRC-specific, and recurrence-free survival. We found significant differences in meat intake depending on the timing of the baseline questionnaire and the treatment that was

TABLE 1
Baseline characteristics of 3122 patients with CRC overall and according to red and processed meat intake and baseline characteristics of the 864 survivors with 5YFU data in the DACHS study[1]

	Red and processed meat intake				Patient characteristics		
Baseline characteristics	<1 time/d (n = 1053)	1 time/d (n = 1219)	>1 time/d (n = 850)	P^2	Total study population[3] (n = 3122)	Subgroup of survivors with 5YFU[4] (n = 864)	P^5
Age, y				0.03			<0.0001
30–59	200 (19.0)	229 (18.8)	192 (22.6)		621 (19.9)	204 (23.6)	
60–69	335 (31.8)	371 (30.4)	292 (34.4)		998 (32.0)	349 (40.4)	
70–79	342 (32.5)	425 (34.9)	250 (29.4)		1017 (32.6)	263 (30.4)	
≥80	176 (16.7)	194 (15.9)	116 (13.6)		486 (15.6)	48 (5.6)	
Sex				<0.0001			0.35
Male	448 (42.6)	779 (63.9)	626 (73.7)		1853 (59.3)	528 (61.1)	
Female	605 (57.5)	440 (36.1)	224 (26.4)		1269 (40.7)	336 (38.9)	
Education[6]				0.18			0.89
Low	706 (67.3)	849 (69.8)	576 (67.8)		2131 (68.4)	583 (67.6)	
Intermediate	186 (17.7)	199 (16.4)	128 (15.1)		513 (16.5)	147 (17.0)	
High	157 (14.9)	169 (13.9)	146 (17.2)		472 (15.2)	133 (15.4)	
Cancer site[7]				<0.0001			0.19
Proximal colon	382 (36.3)	408 (33.6)	203 (23.9)		993 (31.9)	247 (28.7)	
Distal colon	284 (27.0)	308 (25.4)	256 (30.2)		848 (27.2)	244 (28.3)	
Rectum	386 (36.7)	499 (41.1)	388 (45.8)		1273 (40.9)	371 (43.0)	
Stage at diagnosis (UICC)				0.30			<0.0001
I	216 (20.5)	285 (23.4)	195 (22.9)		696 (22.3)	274 (31.7)	
II	324 (30.7)	371 (30.4)	260 (30.6)		955 (30.6)	292 (33.8)	
III	367 (34.9)	378 (31.0)	260 (30.6)		1005 (32.2)	272 (31.5)	
IV	146 (13.9)	185 (15.2)	135 (15.9)		466 (14.9)	26 (3.0)	
Surgery	1031 (97.9)	1186 (97.3)	821 (96.6)	0.21	3038 (97.3)	847 (98.0)	0.23
Chemotherapy[8]	458 (43.7)	555 (45.8)	407 (48.1)	0.16	1420 (45.7)	349 (40.4)	0.008
Radiotherapy[8]	158 (15.1)	238 (19.6)	186 (22.0)	0.0004	582 (18.7)	175 (20.3)	0.28
BMI,[9] kg/m^2				<0.0001			0.08
<18.5	26 (2.5)	24 (1.9)	16 (1.9)		66 (2.1)	12 (1.4)	
18.5 to <25	451 (43.1)	415 (34.1)	267 (31.5)		1133 (36.4)	284 (33.0)	
25 to <30	392 (37.5)	544 (44.7)	384 (45.3)		1320 (42.5)	382 (44.3)	
≥30	177 (16.9)	233 (19.2)	180 (21.3)		590 (19.0)	184 (21.3)	
Physical activity,[10] lifetime MET-h/wk				0.02			0.05
0–138.5	239 (23.2)	293 (24.3)	241 (28.6)		773 (25.1)	215 (25.3)	
>138.5–206.3	290 (28.2)	300 (24.9)	222 (26.4)		812 (26.4)	191 (22.5)	
>206.3–297.9	268 (26.0)	316 (26.2)	180 (21.4)		764 (24.8)	211 (24.8)	
>297.9	232 (22.6)	297 (24.6)	199 (23.6)		728 (23.7)	233 (27.4)	
Active smoking,[11] lifetime pack-years				<0.0001			0.50
Never	496 (47.6)	489 (40.3)	280 (33.3)		1265 (40.8)	332 (38.8)	
<10	225 (21.6)	267 (22.0)	206 (24.5)		698 (22.5)	208 (24.3)	
10–19	112 (10.7)	173 (14.3)	124 (14.7)		409 (13.2)	119 (13.9)	
20–29	89 (8.5)	121 (10.0)	89 (10.6)		299 (9.6)	90 (10.5)	
≥30	121 (11.6)	164 (13.5)	143 (17.0)		428 (13.8)	106 (12.4)	
Alcohol,[12] lifetime g ethanol/d				<0.0001			0.04
None	253 (24.1)	157 (12.9)	98 (11.6)		508 (16.3)	110 (12.8)	
0.1–5.5	280 (26.7)	238 (19.6)	134 (15.8)		652 (20.9)	179 (20.8)	
>5.5–13.5	200 (19.1)	287 (23.7)	166 (19.6)		653 (21.0)	197 (22.9)	
>13.5–29.5	188 (17.9)	283 (23.3)	177 (20.9)		648 (20.8)	206 (23.9)	
>29.5	128 (12.2)	248 (20.4)	273 (32.2)		649 (20.9)	169 (19.6)	
Red and processed meat intake							0.60
<1 time/d	—	—	—		1053 (33.7)	293 (33.9)	
1 time/d	—	—	—		1219 (39.1)	323 (37.4)	
>1 time/d	—	—	—		850 (27.2)	248 (28.7)	
Poultry intake[13]				0.11			0.83
<1 time/wk	382 (36.3)	487 (39.9)	344 (40.5)		1213 (38.9)	332 (38.5)	
≥1 time/wk	670 (63.7)	732 (60.0)	505 (59.5)		1907 (61.1)	531 (61.5)	

(Continued)

TABLE 1 (*Continued*)

Baseline characteristics	Red and processed meat intake				Patient characteristics		
	<1 time/d (n = 1053)	1 time/d (n = 1219)	>1 time/d (n = 850)	P^2	Total study population[3] (n = 3122)	Subgroup of survivors with 5YFU[4] (n = 864)	P^5
Vegetable intake[14]				0.08			0.17
<1 time/d	160 (15.2)	165 (13.6)	146 (17.2)		471 (15.1)	114 (13.2)	
≥1 time/d	891 (84.8)	1052 (86.4)	703 (82.8)		2646 (84.9)	748 (86.8)	
Fruit intake[15]				0.13			0.10
<1 time/d	361 (34.3)	466 (38.4)	307 (36.3)		1134 (36.4)	288 (33.5)	
≥1 time/d	691 (65.7)	748 (61.6)	538 (63.7)		1977 (63.6)	573 (66.5)	
Dairy intake[16]				0.002			0.95
<1 time/d	199 (19.0)	284 (23.5)	215 (25.4)		698 (22.5)	194 (22.6)	
≥1 time/d	850 (81.0)	924 (76.5)	632 (74.6)		2406 (77.5)	665 (77.4)	
Whole-grain intake[17]				<0.0001			<0.0001
<1 time/d	578 (55.1)	758 (62.3)	544 (64.0)		1880 (60.3)	448 (51.9)	
≥1 time/d	472 (44.9)	459 (37.7)	306 (36.0)		1237 (39.7)	416 (48.1)	
Diabetes[18]	174 (16.7%)	230 (19.0%)	170 (20.1%)	0.15	574 (18.5)	121 (14.1)	0.003
Hypertension[19]	510 (49.1%)	654 (54.5%)	437 (51.7%)	0.04	1601 (51.9)	419 (48.6)	0.20
Stroke[20]	62 (5.9%)	70 (5.8%)	44 (5.2%)	0.78	176 (5.7)	28 (3.3)	0.005
Myocardial infarction[21]	79 (7.6%)	95 (7.8%)	64 (7.6%)	0.96	238 (7.7)	61 (7.1)	0.58
Heart failure[22]	153 (15.1%)	162 (13.7)	100 (12.1%)	0.18	415 (13.8)	77 (9.2)	0.0005
Hyperlipidemia[23]	336 (33.4%)	363 (31.2)	257 (31.8%)	0.55	956 (32.1)	275 (32.7)	0.50
Family history of CRC[24]				0.22			0.99
Yes	151 (14.4)	163 (13.4)	137 (16.1)		451 (14.5)	125 (14.5)	
No	899 (85.6)	1055 (86.6)	713 (83.9)		2667 (85.5)	739 (85.5)	
Time interval,[25] mo				0.0001			<0.0001
<1	605 (57.5)	644 (52.8)	397 (46.7)		1646 (52.7)	387 (44.7)	
≥1 to ≤6	167 (15.9)	233 (19.1)	168 (19.8)		568 (18.2)	114 (13.2)	
>6	281 (26.7)	342 (28.1)	285 (33.5)		908 (29.1)	365 (42.1)	

[1]Values are n (%). Some percentages do not add up to 100 because of missing data or rounding. CRC, colorectal cancer; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; MET-h, metabolic equivalent task hours; UICC, Union for International Cancer Control; 5YFU, 5-y follow-up.

[2]Derived by using chi-square test for differences in frequencies across groups of red and processed meat.

[3]Patients with CRC with complete data on meat consumption and follow-up information at 3 and/or 5 y.

[4]Subgroup of survivors with complete data on meat consumption at baseline and at 5-y follow-up.

[5]Derived by using chi-square test for differences in frequencies between baseline and follow-up.

[6–24]Data missing for [6]6 patients (baseline) and 1 patient (5YFU), [7]8 patients (baseline) and 2 patients (5YFU), [8]15 patients (baseline), [9]13 patients (baseline) and 2 patients (5YFU), [10]45 patients (baseline) and 14 patients (5YFU), [11]23 patients (baseline) and 9 patients (5YFU), [12]12 patients (baseline) and 3 patients (5YFU), [13]2 patients (baseline) and 1 patient (5YFU), [14]5 patients (baseline) and 2 patients (5YFU), [15]11 patients (baseline) and 3 patients (5YFU), [16]18 patients (baseline) and 5 patients (5YFU), [17]5 patients (baseline), [18]21 patients (baseline) and 6 patients (5YFU), [19]38 patients (baseline) and 6 patients (5YFU), [20]12 patients (baseline) and 2 patients (5YFU), [21]22 patients (baseline) and 4 patients (5YFU), [22]104 patients (baseline) and 23 patients (5YFU), [23]146 patients (baseline) and 22 patients (5YFU), and [24]4 patients (baseline).

[25]Time interval between diagnosis and interview.

occurring at the time of FFQ completion. In addition, there was a dramatic reduction in the consumption of red and processed meat among CRC survivors at the 5-y follow-up.

In contrast to the large number of studies that investigated the relation between red and processed meat and CRC risk (27–31), to our knowledge only one study has specifically investigated the association of red and processed meat intake and survival in patients with CRC (5). In contrast to our results, red and processed meat intake before CRC diagnosis was associated with a higher risk of all-cause mortality, although predominantly from non-CRC causes. In accordance with our results, the authors did not find an association with CRC-specific mortality (5). Although we could not confirm the results, McCullough et al. (5) found that red and processed meat intake before CRC diagnosis was associated with higher risks of death as a result of CVD (highest compared with lowest quartile; RR: 1.63; 95% CI: 1.00, 2.67). It is possible that we were not able to detect an association due to a lower number of deaths from causes other than CRC (40% compared with 60%), younger age at CRC diagnosis (68 compared with 73 y), shorter follow-up time (4.8 compared with 7.5 y), or differences in study designs (prediagnostic diet assessed before diagnosis compared with prediagnostic diet assessed shortly after diagnosis).

In subgroup analyses, a higher prediagnostic red and processed meat intake was significantly associated with better prognosis in patients with rectal cancer, and CRC-specific survival was improved for patients with stage I–II CRC. Considering that we did not find an association between prediagnostic red and processed meat intake and overall survival among patients with CRC, these results could be due to chance because of the lower number of patients and events in the subgroup analyses or because of multiple testing of the different subgroups. Two previous studies found that among those with a family history of CRC, patients who consumed the highest amount of meat showed reduced all-cause mortality compared with those with lower consumption (5, 6). Although the number of events among those with a family

TABLE 2
Association between red and processed meat intake and overall, CRC-specific, CVD-specific, non–CRC-specific, and recurrence-free survival among stage I–III patients[1]

	Red and processed meat intake													
	<1 time/d				1 time/d				>1 time/d				Per increase in group	
Outcome	*n*	Events, *n* (%)	HR	95% CI	*n*	Events, *n* (%)	HR	95% CI	*n*	Events, *n* (%)	HR	95% CI	HR	95% CI
Overall survival	907	181 (20)			1034	208 (20)			715	113 (16)				
Model 1			1.00	Ref			1.02	0.83, 1.25			0.84	0.66, 1.08	0.93	0.83, 1.04
Model 2			1.00	Ref			1.04	0.85, 1.28			0.85	0.67, 1.09	0.93	0.83, 1.05
CRC-specific survival[2]	906	119 (13)			1029	110 (11)			714	67 (9)				
Model 1			1.00	Ref			0.82	0.60, 1.12			0.88	0.67, 1.14	0.90	0.78, 1.05
Model 2			1.00	Ref			0.91	0.70, 1.19			0.83	0.61, 1.14	0.92	0.78, 1.07
CVD-specific survival	907	27 (3)			1034	48 (5)			715	20 (3)				
Model 1			1.00	Ref			1.47	0.91, 2.38			0.95	0.53, 1.71	0.99	0.76, 1.30
Model 2			1.00	Ref			1.46	0.90, 2.37			0.92	0.51, 1.68	0.97	0.74, 1.28
Non–CRC-specific survival	907	62 (7)			1034	98 (9)			715	46 (6)				
Model 1			1.00	Ref			1.28	0.93, 1.77			0.90	0.61, 1.34	0.97	0.81, 1.16
Model 2			1.00	Ref			1.27	0.92, 1.76			0.88	0.59, 1.30	0.95	0.79, 1.14
Recurrence-free survival[2]	903	175 (19)			1032	195 (19)			714	129 (18)				
Model 1			1.00	Ref			0.98	0.79, 1.22			0.97	0.76, 1.24	0.99	0.87, 1.11
Model 2			1.00	Ref			1.00	0.81, 1.25			1.03	0.80, 1.33	1.02	0.90, 1.15

[1]HRs were obtained from Cox proportional hazards models. Model 1 was adjusted for age at diagnosis, sex, and cancer stage. Model 2 was adjusted for age at diagnosis, sex, cancer stage, chemotherapy, surgery, BMI, physical activity, diabetes, stroke, heart failure, myocardial infarction, dairy intake, whole-grain intake, time between diagnosis and interview, and a time-dependent effect of chemotherapy × log(time). CRC, colorectal cancer; CVD, cardiovascular disease; Ref, reference category.

[2]Data were missing for 7 patients.

history of CRC was larger in our study (n = 66), we could not confirm these results.

To our knowledge, this is the first study to report associations between red and processed meat intake and survival by molecular pathologic subtypes. Higher prediagnostic red and processed meat intake was significantly associated with worse prognosis in patients with *KRAS* mutations. One previous study observed a higher risk of *KRAS*-mutated CRC but not of *KRAS*–wild-type CRC associated with higher heme-iron intake, suggesting that there could be molecular heterogeneity of a potential heme-iron effect (32). However, because our study is the first study on survival and because we did not observe a significant effect modification by *KRAS* status, it is difficult to draw a conclusion. Future studies or meta-analyses will show whether this result can be confirmed.

In this study, we found significant differences in self-reported meat intake depending on the timing of the baseline questionnaire

TABLE 3
Association between red and processed meat intake and overall survival by molecular pathologic subtypes among stage I–III patients[1]

	Red and processed meat intake								
	<1 time/d				≥1 time/d				
Molecular pathologic subtype	*n*	Events, *n* (%)	HR	95% CI	*n*	Events, *n* (%)	HR	95% CI	P^2
MSS	316	77 (24)	1.00	Ref	600	145 (24)	1.07	0.78, 1.50	0.72
MSI-high	39	10 (26)	1.00	Ref	71	15 (21)	0.96	0.30, 3.17	
CIMP-low/negative	316	76 (24)	1.00	Ref	618	147 (24)	1.01	0.74, 1.39	0.41
CIMP-high	46	12 (26)	1.00	Ref	80	20 (25)	1.59	0.61, 4.17	
KRAS–wild-type	216	54 (25)	1.00	Ref	439	99 (23)	0.92	0.63, 1.35	0.09
KRAS-mutated	90	20 (22)	1.00	Ref	176	56 (32)	1.99	1.10, 3.56	

[1]HRs were obtained from Cox proportional hazards models. The multivariable model adjusted for age at diagnosis, sex, cancer stage, chemotherapy, surgery, BMI, physical activity, diabetes, stroke, heart failure, myocardial infarction, dairy intake, whole-grain intake, time between diagnosis and interview, and a time-dependent effect of chemotherapy × log(time). CIMP, CpG island methylator phenotype; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MSI, microsatellite instability; MSS, microsatellite stable; Ref, reference category.

[2]P value for interaction of molecular subtype and red and processed meat consumption after including a multiplicative term into the Cox proportional hazards regression model.

TABLE 4
Ordinal polytomous logistic regression models for odds of consuming higher amounts of red and processed meat depending on the timing of the baseline questionnaire[1]

	Red and processed meat intake, *n* (%)						
Timing of questionnaire	<1 time/d	1 time/d	>1 time/d	P^2	OR[3]	95% CI	P^4
Patients with stage I–III CRC[5]							
<1 mo	513 (37.5)	530 (38.7)	327 (23.9)		1.00	Ref	
≥1 to ≤6 mo	143 (29.1)	206 (41.9)	143 (29.1)	0.0003	1.28	1.06, 1.56	0.01
>6 mo	251 (31.6)	298 (37.5)	245 (30.9)		1.30	1.11, 1.54	0.001
P-trend[6]						0.006	
Patients with stage II–III CRC who had chemotherapy							
Before surgery	24 (34.8)	27 (39.1)	18 (26.1)		0.99	0.61, 1.59	0.96
After surgery but before start of chemotherapy	158 (37.5)	156 (37.1)	107 (25.4)	0.12	1.00	Ref	
Between chemotherapy start and chemotherapy end	37 (24.7)	59 (39.3)	54 (36.0)		1.73	1.22, 2.46	0.002
After chemotherapy ended	91 (34.9)	99 (37.9)	71 (27.2)		1.12	0.84, 1.49	0.46

[1]CRC, colorectal cancer; Ref, reference category.
[2]*P* values derived by using chi-square test for differences in frequencies across groups of red and processed meat.
[3]Adjusted for age, sex, and cancer stage.
[4]*P* value of the Wald chi-square statistic.
[5]Time interval between diagnosis of CRC and completion of the questionnaire.
[6]*P* value calculated by modeling time in months as a continuous variable.

and the treatment that was occurring at the time of FFQ completion. Although the FFQ asked patients to report their dietary intake in the 12 mo before CRC diagnosis, we hypothesized that patients were reporting their current dietary intake at the time of completion, and those who reported their intake within 1 mo of diagnosis had reduced their dietary intake. In analyses of overall survival, patients who completed the questionnaire within 1 mo of their diagnosis and who reported consuming the highest amount of red and processed meat had an improved prognosis, as did those who completed the questionnaire after their surgery but before the start of chemotherapy. However, because patient numbers were small in stratified groups, these results could be due to chance. Furthermore, because the majority of patients reported a dramatic decrease in red and processed meat consumption at the 5-y follow-up compared with reported meat intake in the 12 mo before diagnosis, patients who survive might actually change their diet after a CRC diagnosis. Some studies suggest that cancer survivors make "healthier" dietary and lifestyle changes; however, limited evidence exists specifically for CRC survivors (13–15). Our findings are comparable to a recent study from The Netherlands, which found that after 7 y on average, most CRC survivors reported consuming less meat since CRC diagnosis (33). It is possible that dietary recommendations after diagnosis influenced patients, which may explain changes in dietary habits. Existing recommendations for cancer survivors generally follow the recommendations for cancer prevention because the available evidence with regard to the prognostic impact of diet and dietary changes is limited (29, 34). Ideally, several dietary measurements both pre- and postdiagnostically are required to gather a clearer picture of changes that occur before and after CRC diagnosis and to evaluate the potential impact of red and processed meat on survival.

The strengths of our study include the analysis of a large population-based study sample, the comprehensive adjustment for confounders, and completeness of follow-up. This study adds to the limited evidence on the role of red and processed meat in relation to CRC survival and provides results for overall and cause-specific mortality as well as for recurrence-free survival, which has not been reported previously. We were also able to examine overall survival by some major molecular pathologic subtypes that were currently available in our study population. Despite the large size, compared with McCullough et al. (5) our

TABLE 5
Comparison of red and processed meat intake at baseline with red and processed meat intake at 5-y follow-up among survivors with available 5-y follow-up information on meat intake[1]

	Red and processed meat intake at 5-y follow-up, *n* (%)				
Red and processed meat intake at baseline	<1 time/d	1 time/d	>1 time/d	Total, *n* (%)	κ (95% CI)
<1 time/d	270 (92.1)	20 (6.8)	3 (1.0)	293 (33.9)	
1 time/d	270 (83.6)	48 (14.9)	5 (1.6)	323 (37.4)	0.10 (0.07, 0.13)
>1 time/d	174 (70.2)	57 (23.0)	17 (6.8)	248 (28.7)	
Total	714 (82.6)	125 (14.5)	25 (2.9)	864 (100)	

[1]Red and processed meat intakes at baseline and at 5-y-follow-up were compared by using Cohen's κ coefficient. Agreement of meat intake at baseline and at 5-y follow-up (concordance): 335/864 = 39%.

study had limited power to detect significant weak associations. Furthermore, the FFQ used in our study has not been previously validated, did not assess serving sizes, and was limited in the number of items in each food group. Because of these limitations, it is possible that some misclassification occurred when assigning patients into groups of prediagnostic red and processed meat intake. However, we also tried different groupings of red and processed meat categories, which in no way changed the results. Finally, although we adjusted our Cox models for a range of potential confounders, residual confounding may still be present.

In conclusion, red and processed meat intake before CRC diagnosis was not associated with increased mortality among patients with CRC. Our findings with regard to molecular pathologic subtypes warrant further investigation, especially on the role of *KRAS*. Future studies should aim to examine dietary intake at a number of time points both before and after CRC diagnosis to evaluate dietary changes and their impact on survival and other health outcomes.

We thank Ute Handte-Daub, Ansgar Brandhorst, and Petra Bächer for their excellent technical assistance. We also thank the following hospitals and cooperating institutions that recruited patients for this study: Chirurgische Universitätsklinik Heidelberg, Klinik am Gesundbrunnen Heilbronn, St. Vincentiuskrankenhaus Speyer, St. Josefskrankenhaus Heidelberg, Chirurgische Universitätsklinik Mannheim, Diakonissenkrankenhaus Speyer, Krankenhaus Salem Heidelberg, Kreiskrankenhaus Schwetzingen, St. Marienkrankenhaus Ludwigshafen, Klinikum Ludwigshafen, Stadtklinik Frankenthal, Diakoniekrankenhaus Mannheim, Kreiskrankenhaus Sinsheim, Klinikum am Plattenwald Bad Friedrichshall, Kreiskrankenhaus Weinheim, Kreiskrankenhaus Eberbach, Kreiskrankenhaus Buchen, Kreiskrankenhaus Mosbach, Enddarmzentrum Mannheim, Kreiskrankenhaus Brackenheim, and the Cancer Registry of Rhineland-Palatinate, Mainz. We are also very grateful for the support of the pathologies in the provision of tumor samples: Institut für Pathologie, Universitätsklinik Heidelberg; Institut für Pathologie, Klinikum Heilbronn; Institut für Angewandte Pathologie, Speyer; Pathologisches Institut, Universitätsklinikum Mannheim; Institut für Pathologie, Klinikum Ludwigshafen; Institut für Pathologie, Klinikum Stuttgart; Institut für Pathologie, Klinikum Ludwigsburg. Special thanks to the tissue bank of National Center for Tumor Diseases, Heidelberg, for storage and processing of the tissue samples.

The authors' responsibilities were as follows—PRC, JC-C, H Brenner, and MH: designed the research; LJ, VW, JC-C, H Brenner, and MH: conducted the research; MK, WR, H Bläker, JC-C, H Brenner, and MH: provided essential materials; PRC and MH: analyzed the data, wrote the manuscript, and had primary responsibility for final content; and all authors: critically reviewed the manuscript and read and approved the final manuscript. The authors disclosed no potential conflicts of interest.

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