Adolescent Milk Fat and Galactose Consumption and Testicular Germ Cell Cancer

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Abstract

Recent case-control studies suggested that dairy product consumption is an important risk factor for testicular cancer. We examined the association between consumption of dairy products, especially milk, milk fat, and galactose, and testicular cancer in a population-based case-control study including 269 case and 797 controls (response proportions of 76% and 46%, respectively). Dietary history was assessed by food frequency questions for the index persons and through their mothers including diet 1 year before interview and diet at age 17 years. We used conditional logistic regression to calculate odds ratios as estimates of the relative risk (RR), 95% confidence intervals (95% CI), and to control for social status and height. The RR of testicular cancer was 1.37 (95% CI, 1.12-1.68) per additional 20 servings of milk per month (each 200 mL) in adolescence. This elevated overall risk was mainly due to an increased risk for seminoma (RR, 1.66; 95% CI, 1.30-2.12) per additional 20 milk servings per month. The RR for seminoma was 1.30 (95% CI, 1.15-1.48) for each additional 200 g milk fat per month and was 2.01 (95% CI, 1.41-2.86) for each additional 200 g galactose per month during adolescence. Our results suggest that milk fat and/or galactose may explain the association between milk and dairy product consumption and seminomatous testicular cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2189–95)

Introduction

Testicular cancer is a rare disease. However, it is the most frequent malignancy in young men, and the incidence has been reported to have increased in several populations, including the Germans (1, 2). The highest rates are seen for men in the age group 25 to 34 years.

Several studies focusing on exposures during childhood or even during the prenatal and perinatal periods indicate that carcinogenic effects most likely act very early in life and therefore result in the unusual young adult incidence peak of testicular cancer (3, 4). Cryptorchidism and a familial history of testicular cancer are among the best established risk factors of testicular cancer (5).

Three recent case-control studies showed an association between dietary factors and testicular cancer (6-8). Sigurdson et al. (7) found that high fat consumption 1 year before diagnosis of testicular cancer was associated with an increased risk of testicular cancer. Garner et al. (8) found that high dairy product intake 2 years before interview was associated with an increased risk of testicular cancer. Davies et al. (6) found that milk consumption in adolescence increases the risk of testicular cancer.

A recent ecologic analysis of dietary practices and testicular cancer showed close correlations between milk and cheese consumption and the incidence of testicular cancer (9). These findings and Davies et al.'s (6) study prompted us to explore the association between milk fat consumption in adolescence and testicular cancer because fat consumption has been associated with various types of cancer (10). In addition, we studied the association between adolescent galactose consumption and testicular cancer because galactose, which is one component of the disaccharide lactose, may be toxic on the gonades and galactose metabolism may affect the structure of gonadotropins (11), which are suspected to be involved in the etiology of testicular cancer (12).

Materials and Methods

Several details of the study have been published elsewhere (13-17). Briefly, eligibility criteria for cases included diagnosis of testicular cancer or extragonadal germ cell tumors between July 1995 and December 1997, being between 15 and 69 years of age at the time of diagnosis and being linguistically competent to complete the personal interview. The study area comprised five German geographic regions (cities of Bremen, Essen, Hamburg, Saarbrücken, and the Federal State of Saarland) covering a population of ~1.5 million male residents in the age range of 15 to 69 years at risk. Cases were ascertained through an active reporting system of clinical and pathologic departments in the study regions. In addition, cases in Hamburg were identified through the Hamburg Cancer Registry. A reference pathologist independently assessed the diagnoses by reexamination of tissue specimens including slides or tissue blocks. Tumor histologies were grouped according to Parkin et al. (18).

Case interviews were conducted with 269 of the 353 eligible patients (thereof 2 surrogate interviews with closest relatives) resulting in a response proportion of 76% according to the definition of Slattery et al. (19). Reasons for nonparticipation were refusal (23 cases), our inability to contact cases because the treating physicians refused contacting the cases (37 cases), and other reasons (24 cases).

Controls matching on age (5 year groups) and region (five strata) were randomly selected from mandatory lists of residence. For statistical reasons (power), we strove for a matching ratio of 1:2 cases to controls in the age range 15 to 34

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years and 1:4 cases to controls in the age range 35 to 69 years. Due to these varying matching ratios, controls were on average older than cases. Of all 1,985 eligible controls, 918 (thereof 8 surrogate interviews with closest relatives) were interviewed resulting in a response proportion of 46%. Reasons for nonparticipation were refusal (515 controls), our inability to contact controls because they were never reached at home (149 controls) or moved away from the study region (354 controls), and other reasons (49 controls). We excluded 121 control interviews from the analysis because no matched cases were available in the corresponding strata, leaving 797 control interviews for the analysis.

Data were collected from study participants by interviewers trained specifically for this project. They were blinded to specific study hypotheses as they administered structured questionnaires and were monitored throughout the study to ensure uniform quality of the questionnaire data. The interview took ~70 minutes to complete.

In addition, questionnaires were mailed to the living mothers if an informed consent of the interviewees was obtained. One hundred sixty-eight mothers of the 269 interviewed cases sent back the questionnaire. Nonparticipation was caused by 66 mothers who have died, 12 refusals by the sons, 8 refusals by the mothers, 3 mothers too old or ill, and 12 mothers with other reasons. Three hundred forty-two mothers of the interviewed 797 controls sent back the questionnaire. Nonparticipation was caused by 180 mothers who had died, 90 refusals by the sons, 69 refusals by the mothers, 21 mothers who moved away or were living in foreign countries, 17 mothers too old or ill, and 78 mothers with other reasons. We excluded 29 questionnaires from mothers of controls because no matched questionnaires from mothers of cases were available in the corresponding strata, leaving 168 case and 313 control maternal questionnaires for the analysis.

Exposure Assessment. The dietary section of the interview (index persons) consisted of 23 semiquantitative food frequency questions in reference to the preceding year of the interview. All dietary questions had seven frequency categories (never, once per month, 2-3 times per month, once per week, 2-4 times per week, daily, more than once per day). We assigned average numbers of servings per month to the frequency categories: ''2-3 times per month,'' 2.5 servings per months; ''once per week,'' 4 servings per month; ''2 to 4 times per week,'' 13 servings per month; ''daily,'' 30 servings per month; and ''more than once per day,'' 40 servings per month.

The food items were meat, liver, liver sausage, other sausage/ham, fish, eggs, curd cheese, cheese (spread), cheese on servings, yoghurt, milk, low-fat milk, cacao, butter, cream, vegetables, spinach, kale, carrots, salad (overall number of servings including field salad, chicory or tomato salad), apples, oranges, and any other fresh fruits as a group. Standard portion sizes were stated for milk, low-fat milk, yoghurt and cocoa (200 mL), apples, oranges, and eggs (one item each). In addition, subjects were asked whether, at age 17 years, the consumption was ''more,'' ''about the same,'' or ''less'' than 1 year before interview for the food items milk, cream, yoghurt, cheese, apples, oranges, salad, and meat as has been asked by Davies et al. (6) in their case-control study.

The estimates of food consumption at age 17 years were based on the information of the consumption of the preceding year of the interview in combination with the semiquantitative ratings (''more,'' ''less,'' ''about the same'') for a subset of items including milk, cream, yoghurt, cheese, apples, oranges, salad, and meat. We obtained the consumption at age 17 years by adjusting the consumption at 1 year before interview on the semiquantitative food frequency scale by +/− one category if the consumption at age 17 years was ''more'' or ''less'' as compared with the consumption 1 year before interview. For example, a subject who reported drinking once per week a glass of milk 1 year before interview and who stated that he drank more milk at the age of 17 years was assigned the adjacent next higher frequency category (two to four times per week) for the consumption at age 17 years. We did not construct new categories at the extremes of the ordinal scale. This analysis is called ''categorical shift'' throughout the article. Spearman correlation coefficients between food frequencies 1 year before interview and at age 17 years ranged from 0.62 (meat) to 0.90 (oranges).

In a separate analysis, we based our relative risk (RR) estimates for adolescent food consumption on the maternal questionnaires. Mothers were asked about the dietary habits of their sons at age 17 years by applying a food frequency questionnaire containing the items meat, fish, eggs, cheese, yoghurt, cocoa, milk, low-fat milk, vegetables, salad, apples, and oranges with the same frequency categories as the questionnaires for the sons.

Meat fat, milk fat, and galactose consumptions (grams per month) were computed by assigning standard portion sizes and empirical amounts of fat and galactose to the food items based on the German food database (ref. 20; a detailed description is available on request).

Body mass index was based on self-reported height (centimeter) and weight (kilogram) 1 year before interview. A history of cryptorchidism was rated as positive if interviewees reported that they ever had an undescended testis. A family history of testicular cancer was rated as positive if brothers or the father of the index person was affected with testicular cancer.

Social class was assessed on the basis of years at school (≤9, 10, 11, 12, 13 years) and highest post-school professional degree (none, apprenticeship, university or college degree, others) according to the German recommendations (21).

Statistical Methods. We estimated RRs and corresponding 95% confidence intervals (95% CI) for testicular cancer by conditional logistic regression (PROC PHREG) with SAS version 9.1 (22) taking the matching factors age and region into account. Meat fat, milk fat, and galactose consumption were categorized by quartiles based on the distribution in the control group. Self-reported height and body mass index 1 year before interview were categorized by quartiles based on the distribution in the control group. We evaluated a variety of variables including history of cryptorchidism, family history of testicular cancer, and several food items for potential confounding. We used causal diagrams that are based on the theory of directed acyclic graphs to identify variables that must be controlled to obtain unconfounded effect estimates (23). Based on these diagrams, we adjusted our analyses by height and socioeconomic status. Although a history of cryptorchidism and a family history of cancer are known risk factors for testicular cancer, there is no prior evidence that these factors are associated with the diet at age 17 years. In a sensitivity analysis, we additionally adjusted our effect estimates by the history of cryptorchidism and family history of testicular cancer.

We checked whether the adjustment for meat fat consumption would alter our results for milk fat and galactose consumption. We also assessed whether diet and risk varied by histologic tumor type (seminoma versus nonseminoma).

Results

The interviewed case group consisted of 170 seminomas and 99 nonseminomas of ages 15 to 64 years. One extragonadal seminoma was located in the mediastinum and another extragonadal seminoma in the retroperitoneum. One case suffered from spermatocytic seminoma. Patients with nonseminoma were younger than patients with seminoma (nonseminoma: mean age $\bar{x}$ = 31.1, SD = 8.4; seminoma: $\bar{x}$ = 36.9, SD = 8.8).

Dietary habits were associated with social class in our control group that served as the reference group. Controls who studied at universities had the highest proportion of frequent yoghurt and cream consumption and the lowest proportion of frequent meat, sausages, salad, and egg consumption 1 year before interview. We therefore adjusted all effect estimates for social class as measured by highest professional degree because it was associated with the risk of testicular cancer in our data.

Because height is associated with testicular cancer risk and dietary factors, we also adjusted our effect estimates by self-reported height.

The risk for testicular cancer, especially seminoma, was increased for subjects with professional degrees (i.e., apprenticeship, technical colleges, study at universities and universities for applied sciences). A higher proportion of cases had a history of cryptorchidism resulting in a RR estimate of 4.21 (95% CI, 2.48-7.14). Although based on low prevalences, the risk for testicular cancer was increased for subjects reporting a family history of testicular cancer (father and/or brothers; RR, 5.94; 95% CI, 2.10-16.84; cf. Table 1).

Table 2 displays RR estimates associated with food items consumed during adolescence based on the index persons' interview data (categorical shift). Milk, low-fat milk, cream, and cheese were associated with an increased risk of testicular cancer; the RRs for milk and low-fat milk were increased only for seminoma. Frequent consumption of yoghurt and oranges was associated with decreased risks of testicular cancer. The RR associated with orange consumption was decreased only for seminoma. RR estimates based on the diet 1 year before interview were consistently closer to the null value (RR, 1.0) than estimates based on the diet data that were categorically shifted (e.g., RR for seminoma, 1.42; 95% CI, 1.10-1.83, with each extra 20 milk glasses for the diet 1 year before interview; data not shown).

The analyses of the maternal questionnaire data are presented in Table 3. Although based on small numbers, frequent consumption of eggs, milk, and low-fat milk in adolescence tended to be associated with an increased risk for testicular cancer. Again, the effect of milk was stronger for seminoma than for nonseminoma. Fish, yoghurt, vegetable, and orange consumption tended to be associated with decreased risks of testicular cancer.

Meat fat consumption was only slightly associated with the risk of testicular cancer in all analyses. The largest RR for meat fat consumption existed for the diet at age 17 years (data of the index persons) within the subgroup of seminoma (RR per 200 g/mo, 1.12; 95% CI, 1.00-1.25). All other analyses of meat

Table 1. Self-reported anthropometric measures, history of cryptorchidism, family history of testicular cancer, highest school degree, and post-school professional degree among 269 testicular cancer cases and 797 matching controls

	Complete study			Seminoma			Nonseminoma		
	Cases	Controls	RR* (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Age (y)									
15-24	25	67		4	44		21	67	
25-34	116	301		69	301		47	297	
35-44	96	235		72	235		24	226	
45-54	19	83		15	53		4	48	
55-64	13	111		10	92		3	44	
Self-reported height (cm)†									
≤173	39	185	1.00	29	161	1.00	10	135	1.00
174-178	52	201	0.94 (0.58-1.52)	37	182	0.97 (0.56-1.68)	15	175	1.00 (0.43-2.32)
179-183	83	195	1.64 (1.04-2.58)	49	178	1.35 (0.80-2.30)	34	170	2.60 (1.21-5.59)
≥184	93	210	1.45 (0.92-2.27)	53	199	1.21 (0.71-2.06)	40	196	2.23 (1.05-4.74)
Unknown	2	6		2	5		0	6	
Self-reported body mass index (kg/m^2)†									
≤22.3	78	182	1.00	48	166	1.00	30	172	1.00
[22.3-24.4]	68	188	1.02 (0.68-1.53)	44	175	0.90 (0.55-1.47)	24	165	1.25 (0.67-2.31)
[24.4-26.6]	63	184	1.00 (0.65-1.52)	43	168	0.89 (0.54-1.47)	20	155	1.07 (0.56-2.06)
[>26.6]	49	180	0.96 (0.61-1.51)	29	160	0.73 (0.42-1.47)	20	130	1.45 (0.74-2.84)
Unknown	11	63		6	56		5	60	
Cryptorchidism ever had									
No	226	755	1.00	141	686	1.00	85	643	1.00
Yes	39	27	4.21 (2.48-7.14)	25	26	4.22 (2.30-7.72)	14	26	3.55 (1.74-7.21)
Unknown	4	15		4	13		0	13	
Family history of testicular cancer‡									
No	258	791	1.00	162	720	1.00	96	676	1.00
Yes	11	6	5.94 (2.10-16.84)	8	5	6.65 (2.07-21.34)	3	6	4.06 (0.94-17.50)
Years at school§									
Schoolboy	1	5		0	2		1	5	
≤9	89	304	1.00	60	267	1.00	29	225	1.00
10	61	192	0.84 (0.56-1.25)	39	180	0.84 (0.53-1.35)	22	172	0.82 (0.44-1.52)
12	25	78	0.86 (0.50-1.45)	17	75	0.86 (0.46-1.59)	8	73	0.80 (0.34-1.87)
13	93	217	1.05 (0.72-1.53)	54	200	1.00 (0.63-1.58)	39	206	1.13 (0.64-1.99)
Unknown	0	1		0	1		0	1	
Highest professional post-school degree‖									
None	24	95	1.00	12	88	1.00	12	80	1.00
Apprenticeship	164	485	1.53 (0.93-2.53)	111	446	2.16 (1.09-4.27)	53	400	0.92 (0.46-1.86)
University degree	62	154	1.47 (0.85-2.56)	40	142	1.78 (0.85-3.74)	22	140	1.12 (0.51-2.46)
Other	19	63	0.86 (0.38-1.93)	7	49	1.59 (0.49-5.12)	12	62	0.47 (0.16-1.36)

*RR estimates and 95% CIs are based on the matched evaluation, matching for age and region.

† Height, weight, and body mass index based on self-reported height and weight 1 year before interview.

‡ Father or brothers with testicular cancer.

§≤9: reference group including: no school degree, ''Sonderschulabschluss, Volksschulabschluss, Hauptschulabschluss.''

‖Apprenticeship including technical colleges degrees (''Fachschule''); university or college degrees (''Abitur oder Fachabitur''); others included schoolboys, apprentices, students, people in the community service or military services.

Table 2. RR estimates associated with each extra 20 food item servings per month during adolescence (categorical shift) among 269 testicular cancer cases and 797 matching controls

Food item	Complete study [269:797 (cases/controls)]	Seminoma [170:725 (cases/controls)]	Nonseminoma [99:682 (cases/controls)]
	RR* (95% CI)	RR (95% CI)	RR (95% CI)
Diet at age 17 y			
Meat	1.25 (0.97-1.62)	1.31 (0.97-1.78)	1.00 (0.67-1.49)
Dairy products			
Milk	1.37 (1.12-1.68)	1.66 (1.30-2.12)	0.96 (0.70-1.31)
Low-fat milk	1.25 (0.97-1.62)	1.38 (1.03-1.86)	0.99 (0.64-1.53)
Yoghurt	0.82 (0.62-1.08)	0.77 (0.55-1.07)	0.82 (0.54-1.24)
Cream	1.31 (0.90-1.92)	1.55 (1.01-2.38)	0.92 (0.47-1.79)
Cheese (on servings)	1.42 (0.94-2.16)	1.35 (0.81-2.25)	1.60 (0.86-2.97)
Cheese (spread)	1.27 (0.99-1.63)	1.35 (1.00-1.81)	1.11 (0.75-1.64)
Salad and fruits			
Salad	0.66 (0.49-0.91)	0.64 (0.44-0.94)	0.77 (0.48-1.26)
Apples	0.76 (0.58-1.00)	0.75 (0.54-1.04)	0.93 (0.61-1.42)
Oranges	0.83 (0.58-1.18)	0.71 (0.46-1.12)	1.11 (0.67-1.83)

*All RR estimates and 95% CIs are based on the matched evaluation and are adjusted for highest professional degree and self-reported height 1 year before interview.

fat consumption showed smaller, if any, increases of risk (data not shown).

Tables 4 and 5 present RR estimates for the consumption of milk fat and galactose based on the son's interviews and separately based on the mother's questionnaire data. Milk fat consumption in adolescence was associated with an increased risk of testicular cancer, especially for seminoma (RR, 1.30; 95% CI, 1.15-1.48 per 200 g/mo milk fat in adolescence). Although based on small numbers, the maternal questionnaire data showed a trend towards an increased risk associated with milk fat consumption, especially for seminoma. Galactose consumption was a stronger risk factor for testicular cancer than milk fat consumption for the overall case-control study and especially for seminoma (RR, 2.01; 95% CI, 1.41-2.86 per 200 g/mo galactose in adolescence). Additional adjustment for history of cryptorchidism and family history of testicular cancer did not substantially change our results.

The association between milkfat, galactose consumption at age 17 years, and risk of testicular cancer was stronger among the younger participants ages 15 to 34 years. For example, the estimated seminoma RR per 200 g/mo milkfat consumption (adjusted for highest professional degree and self-reported height) as based on the sons' interviews was 1.45 (95% CI, 1.20-1.75) for the age group 15 to 34 years and 1.17 (95% CI, 0.98-1.40) for the age group 35 to 64 years. Similarly, the estimated seminoma RR per 200 g/mo galactose consumption was 2.98 (95% CI, 1.78-4.97) for the age group 15 to 34 years and 1.37 (95% CI, 0.82-2.30) for the age group 35 to 64 years. Due to the small number of nonseminoma cases, age-stratified analyses (e.g., only 31 nonseminoma cases were of ages 35-64 years) resulted in unreliable effect estimates.

The association between the estimated milkfat and galactose consumption at age 17 based on the son's interview data and on the mother's questionnaire data is presented in Fig. 1. The Spearman correlation coefficient was 0.26 (95% CI, 0.14-0.36) for milkfat and 0.34 (95% CI, 0.23-0.44) for galactose.

Based on the data of consumption 1 year before the interview (control group), we found that certain food items were positively correlated with each other (milk and eggs, milk and butter, milk and yoghurt, vegetables, and salad, etc.). The adjustment for these items did not substantially change our results. For example, adjustment for consumption of meat, liver, eggs, salad, apples, and oranges did not affect the milkfat and galactose findings (e.g., milkfat: seminoma RR, 1.29; 95% CI, 1.11-1.49 per 200 g/mo; galactose: seminoma RR, 2.00; 95% CI, 1.37-2.92 per 200 g/mo in adolescence). The exclusion of

Table 3. RR estimates associated with each extra 20 food item servings per month (adolescent consumption, maternal questionnaires) among 168 testicular cancer cases and 313 matching controls

Food item	Complete study [168:313 (cases/controls)]	Seminoma [104:301 (cases/controls)]	Nonseminoma [64:296 (cases/controls)]
	RR* (95% CI)	RR (95% CI)	RR (95% CI)
Meat, fish, and eggs			
Meat	0.70 (0.39-1.23)	0.85 (0.44-1.67)	0.46 (0.19-1.13)
Other sausage/ham	0.74 (0.49-1.11)	0.71 (0.44-1.14)	0.78 (0.42-1.42)
Fish	0.18 (0.03-0.95)	0.39 (0.06-2.40)	0.03 (0.001-0.74)
Eggs	1.80 (0.89-3.64)	1.99 (0.85-4.68)	1.65 (0.56-4.83)
Dairy products			
Milk	1.21 (0.86-1.70)	1.45 (0.96-2.21)	1.00 (0.62-1.61)
Low-fat milk	1.13 (0.71-1.80)	1.09 (0.62-1.92)	1.29 (0.66-2.49)
Cacao	0.94 (0.66-1.32)	1.06 (0.70-1.60)	0.78 (0.47-1.31)
Yoghurt	0.89 (0.59-1.32)	1.03 (0.64-1.67)	0.73 (0.40-1.31)
Curd cheese	0.89 (0.59-1.36)	0.77 (0.45-1.30)	1.12 (0.64-1.96)
Cheese	0.83 (0.56-1.22)	0.85 (0.53-1.37)	0.79 (0.46-1.38)
Vegetable, salad, and fruits			
Vegetable	0.74 (0.48-1.13)	0.79 (0.47-1.31)	0.70 (0.37-1.30)
Carrots	0.83 (0.48-1.43)	1.01 (0.54-1.89)	0.58 (0.22-1.55)
Salad	1.01 (0.63-1.63)	1.05 (0.59-1.87)	1.08 (0.53-2.19)
Apples	0.98 (0.69-1.39)	0.94 (0.62-1.43)	1.15 (0.70-1.89)
Oranges	0.68 (0.44-1.05)	0.64 (0.37-1.11)	0.77 (0.42-1.39)
Other fresh fruits	0.98 (0.67-1.44)	1.15 (0.73-1.83)	0.82 (0.47-1.43)

*All RR estimates and 95% CIs are based on the matched evaluation and are adjusted for highest professional degree and self-reported height 1 year before interview.

Table 4. Milk fat consumption and testicular cancer

Quartile (g/mo)		Complete study			Seminoma			Nonseminoma		
		Cases	Controls	RR* (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Consumption at age 17 y (index persons)†										
≤411	1	40	159	1.00	25	148	1.00	15	125	1.00
[411-603]	2	36	158	0.84 (0.49-1.42)	21	142	0.81 (0.42-1.54)	15	142	0.86 (0.38-1.93)
[603-833]	3	50	158	1.12 (0.67-1.85)	28	148	1.07 (0.58-1.99)	22	135	1.14 (0.53-2.46)
[833+]	4	82	159	1.80 (1.12-2.89)	57	144	2.48 (1.41-4.37)	25	144	1.15 (0.54-2.46)
Unknown		61	163		39	143		22	136	
RR per 200 g/mo				1.19 (1.07-1.32)			1.30 (1.15-1.48)			1.05 (0.89-1.24)
RR per 200 g/mo‡				1.17 (1.05-1.31)			1.29 (1.13-1.47)			1.03 (0.87-1.22)
Consumption at age 17 y (mothers)§										
≤281	1	24	55	1.00	13	50	1.00	11	51	1.00
[281-469]	2	33	56	1.37 (0.68-2.74)	18	53	1.36 (0.56-3.29)	15	54	1.50 (0.56-4.02)
[469-615]	3	24	55	0.94 (0.44-2.00)	14	54	1.11 (0.43-2.88)	10	55	0.69 (0.23-2.05)
[615+]	4	32	57	1.25 (0.60-2.62)	21	56	2.11 (0.83-5.35)	11	52	0.73 (0.25-2.17)
Unknown		55	90		38	88		17	84	
RR per 200 g/mo				1.07 (0.85-1.35)			1.24 (0.93-1.66)			0.91 (0.66-1.27)
RR per 200 g/mo†				1.07 (0.84-1.36)			1.24 (0.91-1.69)			0.92 (0.66-1.30)

*All RR estimates and 95% CIs are based on the matched evaluation and are adjusted for highest professional degree and self-reported height 1 year before interview.
† Based on all items containing milk fat (including modified items by categorical shift: cheese in bread and meals, yoghurt, milk, low-fat milk and items of the diet 1 year before interview: butter, soft cheese, and cacao).
‡ RR estimates and 95% CIs are based on the matched evaluation and are adjusted for highest professional degree, self-reported height 1 year before interview, a history of familial testicular cancer, and a history of cryptorchidism.
§Based on all items of the maternal questionnaire containing milk fat (milk, low-fat milk, cacao, yoghurt, cheese, soft cheese).

extragonadal germ cell cancers (2 cases), spermatocytic seminoma (1 case), and proxy interviews (10 interviews) did not markedly change our results.

Discussion

In our study, adolescent dairy product consumption (with the exception of yoghurts) and especially milk was a risk factor for testicular cancer, especially for seminoma. We found an increasing risk for seminoma with increasing milk fat intake and an even stronger association between galactose consumption and seminoma especially in the younger men ages 15 to 34 years. Although several epidemiologic studies indicate that risk factors for seminoma and nonseminoma may differ (13, 16, 24-29), it is unclear whether the specificity of the observed effects in our study (no association with nonseminoma risk) is causal or not because the subgroup of nonseminoma patients was small, resulting in imprecise effect estimates.

In their registry-based prevalence case-control study, Davies et al. (6) found that the RR per 1/4 pint of milk per day (i.e., ~120 mL per day) at age 17 years was 1.39 (95% CI, 1.19-1.63). Using the approach of dietary assessment as Davies et al., we found a somewhat lower RR (per 1/4 pint of milk per day: RR, 1.22; 95% CI, 0.99-1.51) when we used the same statistical weighting and the same covariates in our model as Davies et al. Unfortunately, they were not able to stratify their analyses by histologic subgroup. In their recent Canadian case-control study, Garner et al. (8) observed that high dairy product intake was associated with an increased risk of seminoma and nonseminoma. The RR associated with the highest quintile cheese intake was 1.87 for the overall sample and 1.97 for nonseminoma. Although milk intake was associated with an increased risk of testicular cancer, Garner et al. did not

Table 5. Galactose consumption and testicular cancer

Quartile (g/mo)		Complete study			Seminoma			Nonseminoma		
		Cases	Controls	RR* (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Consumption at age 17 y (index persons)†										
≤81	1	39	145	1.00	20	129	1.00	19	114	1.00
[81-168]	2	42	146	1.02 (0.60-1.72)	26	138	1.26 (0.66-2.42)	16	124	0.68 (0.31-1.49)
[168-254]	3	42	146	1.03 (0.61-1.73)	28	134	1.59 (0.82-3.06)	14	131	0.46 (0.20-1.04)
[254+]	4	69	146	1.46 (0.89-2.39)	49	136	2.68 (1.44-4.99)	20	136	0.55 (0.25-1.19)
Unknown		77	214		47	188		30	177	
RR per 200 g/mo				1.33 (0.99-1.78)			2.01 (1.41-2.86)			0.62 (0.38-1.02)
RR per 200 g/mo‡				1.32 (0.97-1.78)			2.02 (1.41-2.91)			0.58 (0.35-0.97)
Consumption at age 17 y (mothers)§										
≤138	1	26	56	1.00	14	51	1.00	12	54	
[138-245]	2	34	56	1.28 (0.64-2.57)	21	53	1.40 (0.57-3.40)	13	52	1.43 (0.53-3.86)
[245-318]	3	20	56	0.73 (0.34-1.55)	8	55	0.56 (0.20-1.59)	12	55	0.92 (0.33-2.54)
[318+]	4	33	56	1.36 (0.66-2.79)	23	55	2.36 (0.94-5.97)	10	52	0.79 (0.28-2.23)
Unknown		55	89		38	87		17	83	
RR per 200 g/mo				1.19 (0.80-1.78)			1.54 (0.93-2.56)			0.92 (0.51-1.66)
RR per 200 g/mo†				1.20 (0.79-1.83)			1.58 (0.92-2.72)			0.93 (0.51-1.68)

*All RR estimates and 95% CIs are based on the matched evaluation and are adjusted for highest professional degree and self-reported height 1 year before interview.
† Based on all food items containing galactose (soft cheese, cheese, yoghurt, milk, low-fat milk, cacao, butter, and cream).
‡ RR estimates and 95% CIs are based on the matched evaluation and are adjusted for highest professional degree, self-reported height 1 year before interview, history of familial testicular cancer, and history of cryptorchidism.
§Based on the items milk, low-fat milk, cacao, soft cheese, and yoghurt.

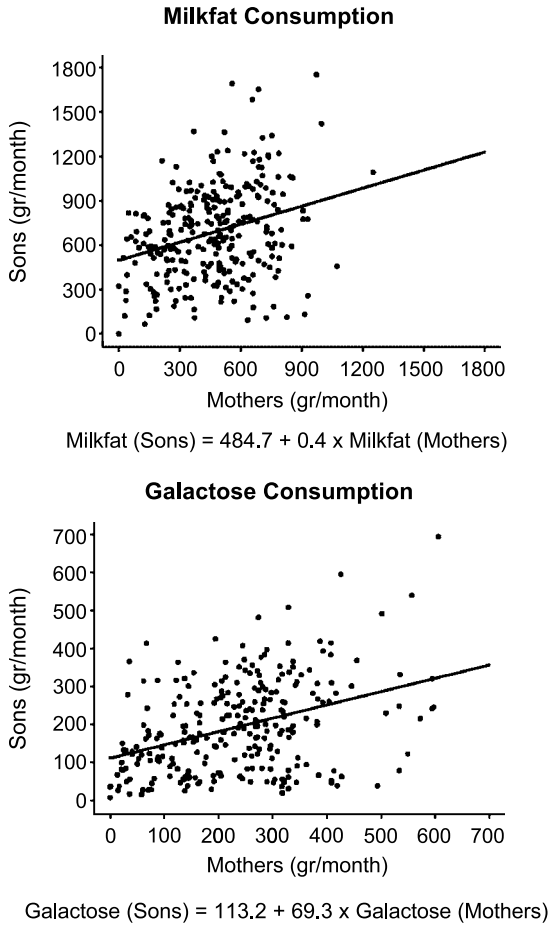

Figure 1. Association between estimated milkfat and galactose consumption during adolescence as reported by the mothers and their sons (grams per month).

observe a monotonic trend by dose (overall sample: P_{trend} = 0.37; seminoma: P_{trend} = 0.36).

Sigurdson et al. (7) showed in a hospital-based case-control study of 160 prevalent cases (46 seminoma and 82 nonseminoma) and 136 friend controls that high fat consumption 1 year before diagnosis increases the risk of testicular cancer. They did not find an association between milk consumption a year before diagnosis and testicular cancer. Methodologic factors may have contributed to their findings. They retrospectively recruited cases treated between 1990 and 1996 at M.D. Anderson Cancer Center and chose friend controls. The proportion of seminoma in the case group (29% only) suggests that the referral pattern to the hospital and the response pattern (38% overall response) of testicular cancer patients were highly selective. The dietary analyses were only based on the diet 1 year before interview and do not account for diet in adolescence.

Ganmaa et al. (9) recently pointed out that the adverse effects of milk on the male testis are only sparsely discussed in the literature. Because diets high in lactose tend also to be high in milk fat, it is difficult to state whether milk fat or galactose may be more potentially harmful. Our observation that galactose consumption shows a stronger association with testicular cancer risk than milk fat consumption may indicate that galactose might be the actual harmful component rather than the milk fat.

Lactose, naturally found only in milk, is a disaccharide composed of galactose and glucose in equal amounts. The precise biological mechanism for the apparent toxicitiy of galactose on the ovary (or gonades in general) has not been defined, but may be another manifestation of the generalized cytotoxicity that occurs in kidney, liver, and brain. Alternatively, disturbed galactose metabolism might affect the structure of the gonadotropins, which include galactose as part of their carbohydrate moiety and thus may preferentially affect the gonades (11).

Several observations suggest an endocrinological etiology of testicular cancer (12, 30, 31). Gonadotropins might be involved in the etiology of testicular cancer and are believed to be responsible for stimulating testosterone production and for triggering spermatogenesis at puberty. Most probably, these hormones act through specific factors that stimulate meiotic division of germ cells. Hypogonadal patients with Kallmann's syndrome who have insufficient gonadtropin secretion never develop testicular cancer despite frequent cryptorchidism (12). Our observed increased seminoma risks in relation to milkfat and galactose, especially in younger men, may support the endocrinological hypothesis. Milk contains, in addition to fats, considerable amounts of estrogens (32). The high estrogen content occurs because present milk cows are mostly pregnant (33). Milk that is nowadays consumed may differ from milk 100 years ago, when pregnant cows did not proficiently produce milk (9).

In contrast to the positive association of seminoma with milk intake, we observed a negative association between frequent yoghurt intake and testicular cancer. One explanation may be that an existing cancer promotion by milkfat or galactose is (over)compensated by probiotic activities of the starter culture, or through the action of anticancerogenic components that were generated in yoghurt by microbial fermentation or proteolysis, like ACE-inhibitory or immunomodulating peptides (34-37).

There are several methodologic factors that may have affected our results. First, it is difficult to speculate about the potential biases inherent in our procedure for selecting controls that resulted in a low response proportion among the controls. The response proportion according to the definition of Slattery et al. (19) is the most conservative calculation method and is not generally accepted by epidemiologists (38). Usually epidemiologists exclude subjects that moved away or died before contact and subjects that were too ill to participate from the response proportion. When we apply this calculation method, the response proportion among cases is 90% and among controls 58%. For the study region Hamburg, we analyzed sociodemographic data (school degree, smoke status, marital status) for a subset of controls who refused to participate in the main interview (97 subjects). We found that participation was associated with a higher school degree (12-13 years at school: 47% participants, 36% nonparticipants) and a higher prevalence of current smokers (52% participants and 39% nonparticipants). We therefore restricted our analyses to cases and controls with lower school degrees (<12 years school) although the selection in favor of the highest school degree may not have operated in all study regions. The associations became only slightly weaker (seminoma RR per 200 g milkfat per month, 1.26; 95% CI, 1.06-1.49; seminoma RR per 200 g galactose per month, 1.70; 95% CI, 1.07-2.69). Furthermore, we found the highest proportion of frequent milk consumers among the controls with the highest school degree. A selection bias in favor of controls with the highest school degree might therefore result in an underestimate of the risk associated with milk consumption. Detailed response analyses by age and region showed that the response was highest in Essen and lowest in Hamburg after adjusting for age. The highest response occurred among men ages 55 to 64 years and was lowest among men ages 45 to 54 years.

A second limitation derives from the general problem of recall of remote diet and potential recall bias in case-control studies (39). Food frequency questionnaires have inherent

limitations in their ability to reproduce individual dietary intakes. Based on German survey data, food items like vegetables, salad, fruits, milk, yoghurt, meat, and fish are regarded as ''important'' or ''very important'' for a healthy lifestyle among the majority of males of ages 18 to 64 years (40). If cases tend to overreport frequent intake of these food items relative to controls, the RR estimates would be biased upwards. The persistence of the milk and milk product effects on seminoma across the data sources (sons and mothers) and the increased risks of only some of the ''worthy'' food items may argue against a strong recall bias in these data. The reconstruction of the food frequencies at age 17 years has not been validated by us and is another limitation. The comparison of the mothers' food frequencies of their sons' diet at age 17 years with the reconstructed food frequencies at age 17 and the food frequencies 1 year before interview based on the sons' interviews showed that the correlation for each item between the mothers and their sons is stronger for the reconstructed food frequencies than for the diet 1 year before interview, which may indicate that the reconstructed food frequencies may provide more valid food frequency estimates of the adolescence diet than food frequencies 1 year before interview.

In conclusion, our study corroborates findings from recent case-control studies that show an association between dairy products and testicular cancer risk. Our exploratory analyses of milk fat and galactose suggest that these dairy products might be responsible for these findings.

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