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Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies

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Pancreatic cancer has few early symptoms, is usually diagnosed at late stages, and has a high case-fatality rate. Identifying modifiable risk factors is crucial to reducing pancreatic cancer morbidity and mortality. Prior studies have suggested that specific foods and nutrients, such as dairy products and constituents, may play a role in pancreatic carcinogenesis. In this

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pooled analysis of the primary data from 14 prospective cohort studies, 2212 incident pancreatic cancer cases were identified during follow-up among 862 680 individuals. Adjusting for smoking habits, personal history of diabetes, alcohol intake, body mass index (BMI), and energy intake, multivariable study-specific hazard ratios (MVHR) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards models and then pooled using a random effects model. There was no association between total milk intake and pancreatic cancer risk (MVHR = 0.98, 95% CI = 0.82–1.18 comparing ≥500 with 1–69.9 g/day). Similarly, intakes of low-fat milk, whole milk, cheese, cottage cheese, yogurt, and ice-cream were not associated with pancreatic cancer risk. No statistically significant association was observed between dietary (MVHR = 0.96, 95% CI = 0.77–1.19) and total calcium (MVHR = 0.89, 95% CI = 0.71–1.12) intake and pancreatic cancer risk overall when comparing intakes ≥1300 with <500 mg/day. In addition, null associations were observed for dietary and total vitamin D intake and pancreatic cancer risk. Findings were consistent within sex, smoking status, and BMI strata or when the case definition was limited to pancreatic adenocarcinoma. Overall, these findings do not support the hypothesis that consumption of dairy foods, calcium, or vitamin D during adulthood is associated with pancreatic cancer risk.
Key words: pancreatic cancer, dairy products, calcium intake, pooled analysis

introduction

Many westernized countries have developed recommendations for dairy and calcium consumption; for example, the United States Department of Agriculture (USDA) recommends that adults consume three servings of dairy foods per day [1, 2]. Milk and dairy consumption has increased worldwide, most dramatically in developing countries, where a doubling of milk intake has occurred over the last 50 years [3].

Dairy foods have been hypothesized to both prevent and promote cancer development, primarily due to nutrients and other bioactive compounds commonly found in dairy products naturally (e.g. calcium) and by fortification (e.g. vitamin D). Milk and other dairy products are the primary source of calcium in Western populations [4]. Prior research has suggested that vitamin D and calcium have anti-carcinogenic properties, such as reducing cell proliferation, angiogenesis and invasiveness, and increasing differentiation and apoptosis [5–8]. However, recent studies have also suggested that other components in dairy, such as select amino acids and proteins, may raise cancer risk through increased mTORC1 signaling [9]. Furthermore, dairy food intake may increase blood concentrations of hormones, such as estrone, progesterone [10], insulin, and insulin-like growth factors [5, 7–10] which have been positively associated with pancreatic cancer risk [11–15], cited in [16].

Previous studies have reported both positive and inverse associations between milk or dairy product intake and cancer risk [17]. In particular, milk has been shown to increase prostate cancer risk [17], but decrease colorectal cancer risk [17]. However, studies examining pancreatic cancer risk have been inconsistent ([18–29], reviewed in [30]). Similarly, the association between dietary vitamin D and circulating vitamin D levels [25 (OH)D], and pancreatic cancer risk are also inconsistent ([31–38], cited in [30]). However, most [27, 33, 38, 39], but not all [40], studies examining calcium intake have suggested an inverse association with pancreatic cancer risk.

In general, studies of dairy, vitamin D, and calcium consumption and of circulating vitamin D levels are not directly comparable because of differences in the actual exposure(s) measured and the contrasts examined. In addition, many prospective cohorts have had limited power to examine pancreatic cancer. In an effort to resolve inconsistencies in the literature, we investigated the associations of intake of dairy products, calcium, and vitamin D with pancreatic cancer risk in a large international consortium of 14 prospective cohorts. We also examined whether the associations differed by environmental, nutritional, and geographic factors.

materials and methods

population

We conducted a pooled analysis within The Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project) [41–44] using the primary data from 14 prospective cohorts [23, 27, 45–54]. The following pre-specified criteria were applied to determine each study's eligibility for inclusion in the pooled analysis: (i) a minimum of 50 incident pancreatic cancer cases diagnosed during the follow-up period, (ii) an assessment of usual diet, (iii) validation of the dietary assessment tool or a closely related instrument, and (iv) prior publication of any diet and cancer association. Studies that fulfilled our inclusion criteria and agreed to participate in the analyses sent their primary data for analysis. The following 14 prospective cohorts were included: Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) [27]; Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP) [46]; Canadian National Breast Screening Study (CNBSS) [48]; Cancer Prevention Study II Nutrition Cohort (CPS II) [49]; California Teachers Study (CTS) [47]; Cohort of Swedish Men (COSM) [54]; Health Professionals Follow-up Study (HPFS) [23]; Iowa Women's Health Study (IWHS) [50]; Melbourne Collaborative Cohort Study (MCCS) [51]; The Netherlands Cohort Study (NLCS) [52]; New York State Cohort (NYSC) [45]; Nurses' Health Study (NHS) [23]; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [53]; and the Swedish Mammography Cohort (SMC) [54] (Table 1). The cohorts represent populations from Europe, North America, and Oceania with a diverse age range of 15–107 years; the majority of cohorts ($n = 12$) enrolled middle-aged individuals and older adults (entrance age ≥40 years old). Eight of the cohorts conducted their baseline assessment during the 1980s, while the remaining completed their baseline assessment during the 1990s. Within each cohort, individuals were followed for a maximum of 7–20 years. The methods for the Pooling Project have been described in detail elsewhere [41–44].

Table 1. Daily mean intakes of dairy foods, calcium and vitamin D by cohort study in the pancreatic cancer analyses in the Pooling Project of Prospective Studies of Diet and Cancer

Cohort[a]	Follow-up years	Baseline cohort size[b]	Case *n*	Mean (SD)[c]								
				Total milk (g/day)	Cheese (g/day)	Cottage cheese (g/day)	Yogurt (g/day)	Ice cream (g/day)	Dietary calcium (mg/day)	Total calcium (mg/day)[d]	Dietary vitamin D (IU/day)	Total vitamin D (IU/day)[d]
Female												
BCDDP	1987–1999	43 162	102	260 (270)	13 (20)	11 (22)	—	19 (35)	861 (369)	1185 (2675)	207 (123)	344 (288)
CNBSS[e]	1980–2000	49 654	105	201 (203)	22 (24)	14 (28)	30 (63)	10 (17)	674 (255)	—	—	—
CPS II	1992–2001	74 138	164	277 (265)	11 (14)	—	44 (71)	7 (19)	884 (380)	1138 (586)	197 (119)	344 (259)
CTS	1995–2003	100 030	116	232 (269)	14 (15)	6 (12)	39 (49)	21 (38)	782 (352)	—	186 (113)	364 (224)
IWHS	1986–2001	34 588	171	275 (266)	11 (13)	19 (30)	11 (38)	11 (19)	749 (286)	1031 (484)	223 (112)	383 (293)
MCCS	1990–2003	22 830	35	—	15 (18)	6 (16)	24 (41)	7 (12)	664 (160)	—	—	—
NLCS[e]	1986–1999	62 573	122	190 (156)	22 (18)	10 (26)	54 (58)	—	871 (256)	—	—	—
NYSC[f]	1980–1987	22 550	48	137 (87)	—	—	—	—	828 (209)	873 (220)	203 (68)	371 (227)
NHS	1986–2002	68 478	178	222 (230)	13 (13)	17 (25)	28 (55)	13 (18)	719 (254)	1068 (496)	183 (100)	322 (244)
PLCO	1993–2004	28 315	60	261 (288)	9 (12)	11 (19)	29 (50)	15 (29)	806 (279)	1243 (529)	172 (92)	505 (359)
SMC	1997–2004	36 630	54	154 (167)	47 (37)	23 (80)	177 (204)	9 (11)	976 (281)	—	171 (63)	—
Male												
ATBC	1984–1999	26 987	204	687 (385)	25 (28)	—	14 (37)	4 (8)	1049 (312)	1052 (314)	175 (91)	209 (200)
CPS II	1992–2001	66 165	210	296 (285)	14 (18)	—	28 (58)	19 (37)	973 (406)	1048 (463)	218 (125)	334 (246)
COSM	1998–2005	45 338	75	311 (334)	75 (60)	4 (27)	178 (245)	14 (16)	1160 (373)	—	221 (100)	—
HPFS	1986–2002	47 778	215	219 (251)	11 (13)	13 (23)	20 (51)	24 (35)	836 (320)	932 (413)	229 (134)	367 (285)
MCCS	1990–2003	14 908	28	—	14 (18)	5 (15)	11 (28)	13 (22)	730 (174)	—	—	—
NLCS[e]	1986–1999	58 279	145	199 (176)	23 (20)	4 (16)	41 (55)	—	933 (291)	—	—	—
NYSC[f]	1980–1987	30 363	90	139 (85)	—	—	—	—	867 (223)	904 (233)	216 (68)	350 (218)
PLCO	1993–2004	29 914	90	301 (349)	10 (14)	9 (18)	13 (35)	25 (39)	929 (316)	1063 (397)	213 (105)	415 (319)

[a]ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BCDDP, Breast Cancer Detection Demonstration Project Follow-up Cohort; CNBSS, Canadian National Breast Screening Study; CPS II, Cancer Prevention Study II Nutrition Cohort; CTS, California Teachers Study; COSM, Cohort of Swedish Men; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Women's Health Study; MCCS, Melbourne Collaborative Cohort Study; NLCS, Netherlands Cohort Study; NYSC, New York State Cohort; NHS, Nurses' Health Study; PLCO, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort.

[b]Baseline cohort size determined after specific exclusions (i.e. prior cancer diagnosis other than non-melanoma skin cancer at baseline, or if they had $\log_e$-transformed energy intakes beyond three standard deviations from the study-specific $\log_e$-transformed mean energy intake of the population). The study population consisted of 319 732 men and 542 948 women among whom 1057 men and 1155 women developed pancreatic cancer.

[c]Studies which have a — did not estimate intake of that nutrient or did not ask on their questionnaire about the consumption of that food item. Whole milk, low-fat milk, skim milk, buttermilk, and evaporated milk contributed to the total milk summary measure. Cheese included cheese (type unspecified), hard cheese, high-fat cheese, and low-fat cheese, while yogurt comprised regular and low-fat yogurt. Milk: an 8 oz serving is equivalent to 245 g; cheese: a 1 oz serving is equivalent to 28 g; cottage cheese: a 0.5 cup serving is equivalent to 105 g; yogurt: a 1 cup serving is equivalent to 227 g; ice cream: a 0.5 cup serving is equivalent to 66 g.

[d]Total calcium and vitamin D intake includes dietary and supplemental sources. Six of the cohorts measured specific calcium supplement intake on their questionnaire (BCDDP, CPS II, HPFS, IWHS, NHS, and PLCO)

[e]The Canadian National Breast Screening Study and the Netherlands Cohort Study were analyzed as case-cohort studies so the baseline cohort size does not reflect the above exclusions.

[f]Since the New York State Cohort had not estimated the amount of calcium in multivitamins, we estimated the contribution of calcium for multivitamin users as 130 mg/day (the calcium value for generic multivitamins that was used in the Nurses' Health Study) to derive total calcium intake from foods and supplements.

assessment of dietary, lifestyle, and medical factors

Usual frequency of consumption of dairy foods was estimated at baseline in each study using a comprehensive food frequency questionnaire (FFQ) or diet history that included 44–276 food items and covered a long period of time, generally the past year. The frequency responses for the food items on the majority of the FFQs ranged from never to multiple times per day. The quantity of each dairy food consumed was converted into grams consumed per day based on the frequency and study-specific serving size for each food item to account for differences in portion sizes across studies.

Most studies estimated nutrient intakes using the food composition method [55]; the New York State Cohort used a 'regression weight' method to estimate nutrient values [45]. The regression-residual method [55] was used to adjust nutrient intakes to an energy intake of 1600 kcal/day for women and 2100 kcal/day for men. Intake of calcium from diet was estimated in all studies, while vitamin D from diet was estimated in 11 cohort studies (Table 1). The use of multivitamins and single supplements was also ascertained by several studies; six of the cohorts measured specific calcium supplement intake on their questionnaire (BCDDP [46], CPS II [49], HPFS [23], IWHS [50], NHS [23], and PLCO [53]). If supplemental intake data were available, total (supplemental and dietary) nutrient intakes were calculated by summing the contributions of that nutrient from dietary, multivitamin, and single supplement sources.

Information on known and suspected pancreatic cancer risk factors was collected on the baseline self-administered questionnaires within each study. Age, height, weight, and smoking status (never, former, or current smoker) were ascertained in all studies. Smoking habits (e.g. smoking duration and number of cigarettes smoked) were ascertained by all studies except The New York State Cohort [45] which instead ascertained the usual number of cigarettes smoked daily and smoking duration. Eleven studies ascertained diabetes status.

outcome assessment

Invasive pancreatic cancer was ascertained by self-report with subsequent medical record review [23], through linkage with cancer registries [45, 47, 48, 50–52, 54], or by both methods [27, 46, 49, 53]. Some studies also identified pancreatic cancer cases through linkage with death registries [23, 45–50, 53]. Of the 2212 invasive pancreatic cancer cases identified, the majority was classified as adenocarcinoma ($n = 1653$ cases) using ICD-O codes 8140–8149, 8160–8169, 8180–8229, 8250–8509, 8520–8560, 8570–8579. Of the remaining 559 pancreatic cancer cases, 266 were of other histologies and 293 did not have histology information or were classified as not otherwise specified (NOS).

exclusions

We excluded individuals if they had a prior cancer diagnosis other than non-melanoma skin cancer at baseline or had $\log_e$-transformed energy intakes beyond three standard deviations of the study- and sex-specific $\log_e$-transformed mean energy intake.

statistical analysis

Dairy foods were modeled categorically and continuously. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by fitting the Cox proportional hazards regression models to data from each study [56]. If there were no cases in the highest intake category in the study, the HR for the highest category could not be estimated in that study and the non-cases in the highest category in that study were included in the second highest category. To test for a linear trend, a continuous variable with values corresponding to the median value for each exposure category was included in the model; the statistical significance of the coefficient for that variable was evaluated using the Wald test.

The models included stratification by age (years) at baseline and the calendar year at the start of follow-up, and treated follow-up time (days) as the time scale. Person-years of follow-up were calculated from the date of baseline questionnaire until the date of pancreatic cancer diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. Multivariable (MV) HRs were adjusted for smoking habits, diabetes, alcohol intake, body mass index (BMI), and energy intake. Because the proportion of participants with missing data for the covariates was generally low (<5%), an indicator variable was used for missing responses, when needed [41].

Study- and sex-specific HRs, weighted by the inverse of the sum of their variance and the estimated between-studies variance component, were pooled using a random effects model [57]. Between-studies heterogeneity was evaluated using the Q statistic [57, 58] and I^2 statistic [59].

To assess whether the association between a dairy food or nutrient and pancreatic cancer risk was linear, we combined the studies into a single data set and used a non-parametric regression analysis [60–62]. If linearity in the association was suggested, we further analyzed that dairy food and/or nutrient as a continuous variable.

To examine variation in HRs by BMI, physical activity, and alcohol consumption, we assessed the statistical significance of the pooled cross-product term between the intake of that specific dairy product or nutrient and the stratification variable using a Wald test. We used meta-regression models [63] to evaluate whether associations varied by sex, smoking status, age at diagnosis, and follow-up time as these are nominal variables or can only be assessed between-studies. We conducted sensitivity analyses excluding the first few years of follow-up to evaluate lag effects (5 years) and to address the possibility of reverse causation due to prediagnostic disease symptoms (2 years). Separate analyses were conducted for adenocarcinomas, as well as for individuals who reported no personal history of diabetes at baseline. These sensitivity analyses were conducted for those studies having more than 10 cases within strata or subgroup being examined. SAS software, version 9.1, was used for all analyses.

results

The study population consisted of 319 732 men and 542 948 women among whom 1057 men and 1155 women developed pancreatic cancer (Table 1). The mean consumption of dairy foods, calcium, and vitamin D varied considerably across

studies. For example, the mean total milk intake ranged from 137 to 687 g/day across the studies.

Total, whole, and low-fat milk intake was not associated with pancreatic cancer risk (Table 2); results were similar when examined in females and males separately. For the same comparison, no statistically significant association was observed when we limited the study population to non-diabetics, never smokers, or when the case definition was limited to adenocarcinomas (results not shown).

Non-statistically significant inverse associations were observed for cottage cheese, yogurt, and ice cream intake with pancreatic cancer risk; risk was similar when examined separately in women and men. In contrast, we observed a significant positive trend in the association for cheese intake and pancreatic cancer risk in females (*P*-value, test for trend = 0.04), but the point estimate for ≥ 50 versus 1–24.9 g/day was not statistically significant (MVHR = 1.36, 95% CI = 0.93–1.98). No statistically significant associations were observed for these dairy foods when the population was limited to never smokers (results not shown).

No statistically significant association was observed between dietary (MVHR = 0.96, 95% CI = 0.77–1.19) and total calcium (MVHR = 0.89, 95% CI = 0.71–1.12) intake and pancreatic cancer risk overall when comparing intakes ≥1300 with <500 mg/day (Table 3). Although the test for between-studies heterogeneity was not statistically significant, the study-specific MVHR, in general, ranged from 0.50 to 2.0 for dietary calcium and total calcium (supplementary Figure S1, available at *Annals of Oncology* online). Results were similar for males and females. Results were also null for the association between dietary and total vitamin D intakes and pancreatic cancer risk. For both dietary calcium and vitamin D, results were similar to the overall results when we limited the analysis to (i) those studies that measured both dietary and total intake and (ii) those individuals with no supplemental calcium or vitamin D intake, respectively.

As suggested by the results of the categorical analyses, when modeling intakes as continuous variables (supplementary Table S1, available at *Annals of Oncology* online), the non-parametric regression analyses were most consistent with a linear, albeit null, association for each dairy food and nutrient intake examined (*P*-value, test for non-linearity >0.10). However, a statistically significant positive association was observed for a 25 g/day increment of cheese and pancreatic cancer risk (MVHR = 1.11, 95% CI = 1.01–1.22; *P* = 0.03).

Overall, the null associations between intakes of total milk, cheese, yogurt, ice cream, total calcium, and total vitamin D with pancreatic cancer risk were not modified by demographic (age, sex), lifestyle (smoking status, alcohol consumption, physical activity, BMI), and cohort (follow-up time) characteristics (*P*-values, test for interaction >0.05; supplementary Table S1, available at *Annals of Oncology* online) or when limited to cases defined as adenocarcinomas or who did not have a personal history of diabetes. However, the associations between pancreatic cancer and cheese (*P*-value, test for interaction = 0.05) and total vitamin D (*P*-value, test for interaction = 0.01) intake were modified by smoking status. A positive association for cheese was observed in former smokers (MVHR = 1.15, 95% CI = 1.05–1.26), while no statistically significant association was observed

Table 2. Pooled age and multivariable[a] (MV) adjusted hazard ratios and 95% confidence intervals for pancreatic cancer according to intake of dairy foods

Food	Categories of intake (g/day)						I^{2b}	P_{HET}*	$P_{Het\ by\ Sex}$**	P_{trend}***
	HR (95% CI)									
Total milk[c,d,e,f]	0	1–69.9	70–124.9	125–249.9	250–499.9	≥500				
Cases (M, F)[g]	82, 108	117, 186	129, 177	268, 339	197, 171	235, 138				
Age HR	1.14 (0.94, 1.39)	1.00 (Ref)	1.04 (0.88, 1.23)	1.01 (0.88, 1.17)	1.04 (0.88, 1.24)	0.92 (0.77, 1.10)	0%	0.75	0.23	0.09
MV HR	1.12 (0.92, 1.37)	1.00 (Ref)	1.08 (0.92, 1.28)	1.06 (0.92, 1.23)	1.09 (0.90, 1.31)	0.98 (0.82, 1.18)	0%	0.91	0.29	0.38
Whole milk[c,h,i,j]	0	1–124.9	125–249.9	≥250						
Cases (M, F)[g]	419, 624	159, 245	62, 107	71, 74						
Age HR	1.00 (Ref)	1.05 (0.93, 1.19)	1.03 (0.86, 1.23)	1.01 (0.83, 1.22)			0%	0.99	0.92	0.92
MV HR	1.00 (Ref)	1.04 (0.92, 1.17)	1.01 (0.84, 1.21)	0.98 (0.80, 1.19)			0%	0.99	0.97	0.65
Low-fat milk[c,j,k,l]	0	1–124.9	125–249.9	≥250						
Cases (M, F)[g]	303, 392	147, 207	142, 185	136, 171						
Age HR	1.00 (Ref)	0.99 (0.84, 1.17)	1.00 (0.86, 1.15)	0.87 (0.75, 1.01)			5%	0.40	0.22	0.06
MV HR	1.00 (Ref)	1.02 (0.87, 1.20)	1.06 (0.92, 1.23)	0.93 (0.80, 1.08)			5%	0.40	0.37	0.38
Cheese[m,n]	0	1–24.9	25–49.9	≥50						
Cases (M, F)[g]	120, 138	573, 721	164, 182	102, 61						
Age HR	0.87 (0.74, 1.01)	1.00 (Ref)	1.03 (0.84, 1.28)	1.26 (0.90, 1.78)			42%	0.05	0.78	0.08
MV HR	0.87 (0.74, 1.01)	1.00 (Ref)	1.07 (0.86, 1.32)	1.26 (0.91, 1.76)			34%	0.11	0.68	0.07
Cottage cheese[o,p,q]	0	1–25.9	26–52.9	≥53						
Cases (M, F)[g]	294, 380	185, 411	45, 101	13, 43						
Age HR	1.00 (Ref)	0.89 (0.77, 1.03)	0.93 (0.76, 1.13)	0.88 (0.61, 1.25)			25%	0.23	0.78	0.59
MV HR	1.00 (Ref)	0.92 (0.79, 1.07)	0.98 (0.80, 1.20)	0.90 (0.64, 1.28)			21%	0.26	0.87	0.94

Yogurt[r,s]	0	1–27.9	28–56.9	≥57				
Cases (M, F)[g]	560, 474	171, 204	71, 118	140, 190				
Age HR	1.00 (Ref)	0.82 (0.72, 0.93)	0.96 (0.78, 1.19)	0.84 (0.73, 0.97)	0%	0.93	0.75	0.08
MV HR	1.00 (Ref)	0.88 (0.77, 0.99)	1.05 (0.86, 1.29)	0.93 (0.81, 1.08)	0%	0.98	0.93	0.70
Ice cream[t,u]	0	1–16.9	17–32.9	≥33				
Cases (M, F)[g]	296, 315	304, 468	85, 112	117, 69				
Age HR	1.00 (Ref)	0.91 (0.79, 1.05)	0.85 (0.71, 1.03)	0.95 (0.79, 1.14)	0%	0.82	0.81	0.40
MV HR	1.00 (Ref)	0.95 (0.83, 1.09)	0.92 (0.77, 1.10)	1.01 (0.84, 1.22)	0%	0.75	0.91	0.88

[a]Multivariable HRs were adjusted for smoking habits (never smokers; past smokers, pack-years <15 years; past smokers, pack-years ≥15 years; current smokers, pack-years <40 years, current smokers, pack-years ≥40 years), personal history of diabetes (no, yes), alcohol intake (0, 0.1–14.9, 15–29.9, ≥30 g/day), BMI (continuously) and energy intake (continuously); age in years and year of questionnaire return were included as stratification variables. For certain dairy food items, to prevent unstable risk estimates, we selected the next highest category as the referent category because the number of cases in the no consumption category was too few.

[b]I^2 statistic describes the percentage of total variation that is due to heterogeneity rather than chance; 0% represents no heterogeneity.

[c]The Melbourne Collaborative Cohort Study was excluded from the milk analyses as this study did not measure milk intake.

[d]The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial male cohort were excluded from the total milk analyses for the 0 g/day category because these studies had no cases in this category. The participants who would have been in this category were included in the 1–69.9 g/day category.

[e]The Iowa Women's Health Study was excluded from the total milk analyses for the 250–499.9 g/day category because this study had no cases in this category. The participants who would have been in this category were included in the 125–249.9 g/day category.

[f]The New York State Cohort was not included in the 250–499.9 and ≥500 g/day categories of milk because this study had no participants in these two categories. The maximum reported milk intake for the New York State Cohort was 207 g/day owing to the frequency response categories on the food frequency questionnaire for milk consumption. The participants who would have been in these categories were included in the 125–249.9 g/day category.

[g]The number of cases for males and females (M, F).

[h]The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and New York State Cohort were not included in the whole milk analyses as they did not measure whole milk intake separately.

[i]Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial female cohort was excluded from the whole milk analysis for the 125–249.9 and ≥250 g/day categories because this study had no cases in these two categories. The participants who would have been in these categories were included in the 1–124.9 g/day category.

[j]Whole milk includes full fat milk and 2% milk. Low-fat milk includes 1% milk and skim milk.

[k]The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and New York State Cohort were not included in the low-fat milk analysis as they did not measure low-fat milk intake.

[l]The Canadian National Breast Screening Study was not included in the low-fat milk analysis due to the small number of cases who were consumers (n<10).

[m]The New York State Cohort was excluded from the cheese analyses as they did not measure cheese intake.

[n]The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial female and male cohorts and The Melbourne Collaborative Cohort Study female cohort were excluded from the cheese analyses for the ≥50 g/day category because they had no cases in this category. The participants who would have been in this category were included in the 25–49.9 g/day category.

[o]The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Cancer Prevention Study II Nutrition Cohort, and New York State Cohort were excluded from the cottage cheese analyses as they did not measure cottage cheese intake.

[p]The Swedish Mammography Cohort was not included in the cottage cheese analyses due to the small number of cases (n<10) who were consumers of cottage cheese.

[q]The Melbourne Collaborative Cohort Study and the Netherlands Cohort Study male cohort were excluded from the cottage cheese analyses for the 26 to <52.9 and ≥53 g/day categories; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial male cohort was also excluded from the ≥53 g/day category because these studies had no cases in these categories. The participants who would have been in these categories were included in the next lowest g/day category.

[r]The Breast Cancer Detection Demonstration Project Follow-up Cohort and New York State Cohort were excluded from the yogurt analyses as they did not measure yogurt intake.

[s]The Melbourne Collaborative Cohort Study male cohort was excluded from the yogurt analyses due to the small number of cases who were consumers (n < 10).

[t]The Netherlands Cohort Study and the New York State Cohort were excluded from the ice-cream analyses as they did not measure ice cream intake.

[u]The Swedish Mammography Cohort was excluded from the ice cream analyses for the ≥33 g/day category because this study had no cases in these categories. The participants who would have been in this category were included in the 17–32.9 g/day category.

*P-value, test for between-studies heterogeneity for the highest category.

**P-value, test for modification of the effect by gender for the highest category using the meta regression method.

***P-value, test for trend.

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Table 3. Pooled age and MV[a] adjusted hazard ratios and 95% confidence intervals for pancreatic cancer according to intake of calcium (mg/day)[b] and vitamin D (IU/day)[b]

Nutrients	Categories of intake						I^2	P_{HET}*	$P_{Het\ by\ Sex}$**	P_{trend}***
	HR (95% CI)									
Dietary calcium[d]	<500	500–699.9	700–899.9	900–1099.9	1100–1299.9	≥ 1300				
Cases (M,F)[e]	61, 179	167, 326	296, 316	240, 178	148, 77	145, 79				
Age HR	1.00 (Ref)	0.88 (0.75,1.03)	0.93 (0.79,1.09)	0.81 (0.68,0.97)	0.78 (0.63,0.97)	0.87 (0.71,1.08)	0%	0.95	0.86	0.13
MV HR	1.00 (Ref)	0.93 (0.79,1.09)	1.02 (0.87,1.20)	0.90 (0.75,1.08)	0.86 (0.69,1.07)	0.96 (0.77,1.19)	0%	0.92	0.87	0.56
Total calcium[f]	<500	500–699.9	700–899.9	900–1099.9	1100–1299.9	≥ 1300				
Cases (M,F)[e]	43, 60	112, 127	211, 151	182, 116	126, 74	135, 195				
Age HR	1.00 (Ref)	0.79 (0.60,1.05)	0.94 (0.75,1.19)	0.79 (0.63,1.00)	0.77 (0.60,0.99)	0.79 (0.63,0.99)	0%	0.92	0.50	0.02
MV HR	1.00 (Ref)	0.84 (0.64,1.11)	1.03 (0.82,1.29)	0.88 (0.70,1.12)	0.86 (0.67,1.10)	0.89 (0.71,1.12)	0%	0.95	0.42	0.21
Dietary vitamin D[g,h]	<100	100–199.9	200–299.9	300–399.9	400–499.9	≥ 500				
Cases (M,F)[e]	106, 151	362, 383	262, 234	102, 80	31, 33	21, 12				
Age HR	1.00 (Ref)	0.97 (0.84,1.12)	0.88 (0.75,1.03)	0.85 (0.69,1.04)	0.86 (0.65,1.15)	0.90 (0.61,1.31)	0%	0.67	0.45	0.04
MV HR	1.00 (Ref)	1.02 (0.88,1.18)	0.94 (0.80,1.10)	0.90 (0.73,1.11)	0.92 (0.69,1.22)	0.94 (0.64,1.38)	0%	0.69	0.53	0.12
Total vitamin D[i,j]	<100	100–199.9	200–299.9	300–399.9	400–499.9	≥500				
Cases (M,F)[e]	84, 90	246, 218	180, 117	74, 66	44, 79	181, 221				
Age HR	1.00 (Ref)	0.97 (0.81,1.16)	0.85 (0.70,1.03)	0.89 (0.70,1.12)	0.90 (0.67,1.22)	0.83 (0.69,1.01)	0%	0.75	0.33	0.10
MV HR	1.00 (Ref)	1.02 (0.85,1.22)	0.90 (0.73,1.10)	0.95 (0.75,1.20)	0.96 (0.70,1.31)	0.91 (0.75,1.09)	0%	0.78	0.47	0.30

[a]Multivariable HRs were adjusted for smoking habits (never smokers; past smokers, pack-years <15 years; past smokers, pack-years ≥15 years; current smokers, pack-years <40 years, current smokers, pack-years ≥ 40 years), personal history of diabetes (no, yes), alcohol intake (0, 0.1–14.9, 15–29.9, ≥30 g/day), BMI (continuously), and energy intake (continuously); age in years and year of questionnaire return were included as stratification variables.

[b]Calcium is based on mg/day and Vitamin D is based on IU/day.

[c]I^2 statistic describes the percentage of total variation that is due to heterogeneity rather than chance; 0% represents no heterogeneity.

[d]The Melbourne Collaborative Cohort Study (male and female cohorts) were not included in the 1100–1299.9 and ≥1300 mg/day categories because this study had no cases in these categories. The participants who would have been in these categories were included in the 900–1099.9 g/day category.

[e]The number of cases for males and females (M, F).

[f]The California Teachers Study, Canadian National Breast Screening Study, Cohort of Swedish Men, Melbourne Collaborative Cohort Study (male and female cohorts), Netherlands Cohort Study (male and female cohorts), and Swedish Mammography Cohort were excluded from the total calcium analyses because they did not have supplement use data available for this nutrient.

[g]The Canadian National Breast Screening Study, Melbourne Collaborative Cohort Study (male and female cohorts), and Netherlands Cohort Study (male and female cohorts) were excluded from the dietary and total vitamin D analyses because they did not have data available for vitamin D.

[h]The Nurses' Health Study was not included in the 400–499.9 and ≥500 IU/day categories because this study had no cases in these categories. The Cohort of Swedish Men, New York State Cohort (male and female cohorts), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (male and female cohorts), and the Swedish Mammography Cohort were not included in the ≥500 IU/day category because they had no cases in this category. The participants who would have been in these categories were included in the next lowest category.

[i]The Cohort of Swedish Men and Swedish Mammography Cohort were excluded from the total vitamin D analyses because they did not have supplement use data available for this nutrient.

[j]The New York State Cohort female cohort was excluded from the total vitamin D analyses as they did not have any cases in the reference category.

*P-value, test for between-studies heterogeneity for the highest category.

**P-value, test for modification of the effect by gender for the highest category using the meta regression method.

***P-value, test for trend.

in never and current smokers. For total vitamin D, an inverse association was noted for never smokers, but not in former and current smokers. Overall, results were similar when we compared results from analyses limited to the first 5 years of follow-up with those of 5 or more years of follow-up, or stratified by the median age at diagnosis of the cases.

discussion

In this pooled analysis of 14 cohort studies, no statistically significant associations were observed between intakes of dairy foods, calcium, and vitamin D during adulthood with pancreatic cancer risk. Generally, these null associations were similar by sex and age, when the analytic sample was limited to non-diabetics or never smokers, and when the outcome was limited to pancreatic adenocarcinomas.

Our findings are consistent with some, but not all, previous findings. In a large systematic review conducted by the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) in 2007 [17, 30, 64], the panel concluded that the evidence for an association between milk and dairy product consumption and pancreatic cancer risk was limited and no conclusions could be drawn regarding these associations. Previous cohort studies, which were not included in our analyses, have reported null and inverse associations with milk intake ([21, 24, 28, 65], cited in [30]); the results for pancreatic cancer from case–control studies were more inconsistent ([29, 66–74], cited in [30]).

Similar to our findings, most prior cohort studies, which were not included in our analyses, and case–control studies reported non-significant associations with cheese consumption ([17, 21, 23, 24, 27, 70, 71], cited in [30]). However, a few previous studies have reported statistically significant or suggestive inverse associations with cheese, yogurt, and sour milk intake ([18, 21, 29, 66] cited in [30]).

Calcium and vitamin D, biologically active compounds found in dairy foods, have been theorized to play both protective and adverse roles in carcinogenesis [6, 9]. Similar to our dairy food results, we observed null associations for intakes of these nutrients and pancreatic cancer risk. For dietary and total calcium intake, our findings were in contrast to the findings from a number of case–control studies ([32, 38], cited in [30]) which generally showed inverse or suggestive inverse associations. However, case–control studies are limited by recall, selection, and survival biases.

Findings from previous studies of pancreatic cancer also have been mixed for vitamin D intake and pancreatic cancer risk ([25, 38, 66, 75, 76], cited in [30]) and for more integrated measures of overall vitamin D status, predicted vitamin D status [31], and circulating 25-hydroxy-vitamin D levels [34–37]. A study of current smokers even suggested a positive association for circulating vitamin D levels [35]. We observed a significant interaction for total vitamin D–pancreatic cancer association (P interaction = 0.01); however, the CIs for the MVHR for each smoking strata included the null. Although individuals who live in latitudes further from the equator will be exposed to less sunlight, we observed no between-studies heterogeneity, even though the studies arose from a large geographic distribution.

Heterogeneity in risk estimates across studies may be the result of differences in the exposure definitions and measurements, comparisons and contrasts, and covariates included in the modeling of the association. An advantage of our study was the ability to harmonize the exposures, covariates, and outcome variables and to model the data using a standardized approach, thereby lessening potential sources of heterogeneity across the 14 cohorts. For each exposure examined, there was no statistically significant between-studies heterogeneity present. In addition, results were similar from the age-adjusted model compared with models adjusted for most of the important known pancreatic cancer risk factors (e.g. smoking history, BMI), suggesting that confounding was minimal.

Compared with an individual cohort study, this pooled analysis had much greater statistical power to evaluate the overall associations between dairy food and nutrient intake and pancreatic cancer risk, and to examine effect modification and subgroup differences. Generally, we observed consistent results when we stratified by suggested or known risk factors for pancreatic cancer, such as smoking, the most consistent risk factor for pancreatic cancer.

The studies included in this pooled analysis measured diet before diagnosis of pancreatic cancer; thus, a strength of this analysis is that a cancer diagnosis would not have influenced the reporting of dairy food and nutrient intake. The validity of dairy product assessment has been moderate to good in validation studies associated with these cohorts (r = 0.30–0.81 [55, 77–88]; A. Wolk, personal communication). However, error in the dietary measurements, due to using only a one-time measure of diet, might have resulted in greater misclassification of usual consumption than if multiple assessments throughout follow-up had been used. However, inaccurate reporting of intake should not have varied by outcome status in this prospective study and, as such, may only have resulted in non-differential misclassification. The effect of non-differential misclassification would have tended to attenuate the associations, and may be a possible explanation for the observed null associations.

In summary, this large pooled analysis provides little support for a role for consumption of dairy foods and their related nutrients at moderate levels of intake during adulthood on risk of pancreatic cancer risk. These results were consistent across the studies included in our analysis giving strength to our overall findings. Given that intake of dairy products and nutrients are not strongly related to pancreatic cancer risk, identification of other modifiable preventive factors is important to reduce pancreatic cancer incidence and mortality.

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disclosure

The authors have declared no conflicts of interest.

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