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Dairy intake and the risk of pancreatic cancer: the Japan Collaborative Cohort Study (JACC Study) and meta-analysis of prospective cohort studies

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Abstract

Dairy product intake was suggested to reduce the risk of gastrointestinal cancers. This study investigated the association between dairy product intake and the risk of pancreatic cancer (PAC) using a prospective cohort study and meta-analysis of prospective cohort studies. First, we included 59 774 people aged 40–79 years from the Japan Collaborative Cohort Study (JACC Study). The Cox regression was used to compute the hazard ratios (HR) and 95 % CI of incident PAC for individuals who reported the highest intakes of milk, cheese and yogurt compared with not consuming the corresponding dairy products. Then, we combined our results with those from other four prospective cohort studies that were eligible after searching several databases, in a meta-analysis, using the fixed-effects model before evaluating publication bias and heterogeneity across studies. In the JACC Study, the highest *v.* no intakes of milk, cheese and yogurt were not associated with the reduced risk of PAC after a median follow-up of 13·4 years: HR (95 % CI) = 0·93 (0·64, 1·33), 0·91 (0·51, 1·62) and 0·68 (0·38, 1·21), respectively. The results did not significantly change in the meta-analysis: 0·95 (0·82, 1·11) for milk, 1·16 (0·87, 1·55) for cheese and 0·91 (0·79, 1·05) for yogurt. The meta-analysis showed no signs of publication bias or heterogeneity across studies. To conclude, consumption of milk, cheese and yogurt was not associated with the risk of PAC either in the JACC Study or the meta-analysis.

Key words: Milk: Cheese: Yogurt: Cancer: Pancreas: Meta-analysis

With 458 918 new cases and 432 242 deaths in 2018, pancreatic cancer (PAC) contributed to 2·5 % of all-cause cancers and 4·5 % of all deaths caused by cancer worldwide. In Japan, a total of 43 119 new cases of PAC and 37 358 related deaths were recorded in the same year representing 4·9 % of all-cause incident cancers and 9·1 % of all cancer deaths in the country, almost twice proportions as the worldwide incidence and mortality[1,2]. It is projected that, over the period between 2018 and 2040, PAC incidence and mortality will increase worldwide by 77·7 % and 79·9 %, respectively[2]. Given its growing incidence and poor five-year survival rate that hardly exceeds 5 %, identifying modifiable risk factors for PAC has become a public health priority to apply risk prevention programmes[3,4].

Despite the complex and multifactorial pathogenesis of PAC[5–7], previous research has suggested that dietary factors may play aetiological roles[8,9]. For example, red and processed meat consumption was shown to increase the risk of PAC due to the carcinogenic effects of *N*-nitroso compounds[10–13], while consuming fruits, vegetables and whole grains reduced that risk because of the anticarcinogenic effects of Ca, Mg, potassium, α- and beta-carotene and vitamins A, B_6 and C contents of these foods[13–17]. In this regard, it could be suggested that the intake of dairy products might be associated with the reduced risk of PAC because they are rich sources of vitamins A, B_{12} and D as well as Ca, Mg and Zn[18–20]. Those vitamins and minerals pose anticarcinogenic properties via inducing cell cycle arrest, apoptosis and differentiation while suppressing angiogenesis, invasion and metastasis[21–24]. Further, dairy products include large amounts of lactic acid bacteria and conjugated linoleic acids[25–27]. Lactic acid bacteria help in enhancing the host's immune response, inducing antioxidative and antiproliferative functions and detoxifying toxicants formed during food processing, characteristics that have been proven to prevent cancer[28–30]. In animal models, lactic acid bacteria were able to alleviate

Abbreviations: HR, hazard ratios; JACC Study, Japan Collaborative Cohort Study; PAC, pancreatic cancer.

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pancreatic inflammation, improve glucose tolerance and prevent pancreatic damage, factors that are closely related to the risk of PAC[31]. Alike, conjugated linoleic acids were shown in pre-clinical and human studies to have potential anticarcinogenic effects[32,33]. Using human cells *in vitro*, diets rich in conjugated linoleic acids were shown to reduce PAC penetrance and repress its proliferation[34].

Many case–control studies were conducted to detect the retrospective association between dairy intake and PAC[35–51]. However, in addition to their conflicting findings, the case–control studies were prone to selection bias attributed to the high and rapid fatality of PAC, thus, researchers, to assess dairy intakes, either recruited the survivors who showed low response rates and posed different socio-demographic and clinical characteristics compared with the deceased or interviewed next-of-kin whom data reliability was considered uncertain. Besides, these studies were subject to bias due to the high possibility of changes in dietary habits among cases after PAC diagnosis. Furthermore, the methodological limitations of these case–control studies did not allow the temporal association between dairy intake and PAC to be investigated[52–54]. To avoid such biases, the associations between the intakes of different dairy products and the risk of PAC were investigated using a few prospective cohort studies[53–59]. Although the dietary habits of Asian people are substantially different from those in Western countries[60], only two prospective studies assessed the possible association between dairy consumption and the risk of PAC among Asians[58,59]. Both studies were conducted on Japanese people and were limited by the small number of participants and the lack of representativeness; one study included 11 349 residents of thirteen rural areas[58] and the other study included 3158 residents of one prefecture[59].

Since the consumption of dairy products is encouraged in Japan to ensure adequate nutrient intake[61] and given the high incidence of PAC in the country[1,2] alongside the limitations of previous national studies[58,59], we used the data of the Japan Collaborative Cohort Study (JACC Study) to investigate the association between the intakes of three dairy products (milk, cheese and yogurt) and the risk of PAC incidence among a large cohort of middle-aged Japanese. This study primarily hypothesised that the intake of dairy products might be inversely associated with the risk of PAC. Then, we conducted a meta-analysis combining the results of the JACC Study with those from previously published prospective cohort studies.

Methods

The Japan Collaborative Cohort Study

Study population and baseline questionnaire. The JACC Study is a prospective cohort study in which baseline data collection was carried out between 1988 and 1990 in forty-five areas in Japan where 110 585 people aged 40–79 years were included. The JACC Study baseline self-administered questionnaire included data about several socio-demographic characteristics, daily walking and leisure physical activity, intakes of common foods and beverages, smoking and alcohol drinking habits and past medical histories[62,63]. The follow-up for cancer incidence was conducted in twenty-four areas using population-based and hospital registries or death certificates before it was terminated by the end of 2009 in four areas, 2008 in two areas, 2006 in two areas, 2003 in one area, 2002 in eight areas, 2000 in one area, 1999 in one area, 1997 in four areas and 1994 in one area[62]. Herein, we excluded people with a positive history of cancer before baseline and people who missed reporting on dairy intake. Eventually, the analysis was confined to 59 774 Japanese people who reported at least one of the three questions assessing dairy intake: 58 656 in milk, 49 302 in cheese and 49 934 in yogurt (Fig. 1).

Exposure, outcome and covariates. Data on dairy intake (exposure) were collected using the self-administered FFQ in the JACC Study baseline questionnaire: *'How frequently do you consume the following items?'*. These items included dairy products in the form of '*milk*', '*cheese*' and '*yogurt*' among other common foods. The available responses were as follows: '*never*', '*one to two times/month*', '*one to two times/week*', '*three to four times/week*' and '*almost every day*'. A validation study among a subsample of the JACC Study's participants showed good validity and reproducibility of the three investigated items; the Spearman rank correlation coefficients between two frequencies assessed twice apart one year were 0·69 for milk, 0·57 for cheese and 0·54 for yogurt (P-values < 0·001) and between the frequencies and the weighed dietary record were 0·65 for milk, 0·44 for cheese and 0·58 for yogurt (P-values < 0·001)[64]. The median portion size of the intakes of the three dairy products per day was estimated in the same validation study and was found to be 146 g for milk, 17 g for cheese and 98 g for yogurt[64]. Therefore, the five frequencies in our study could be roughly converted into the following amounts: ((milk: 0·0, 6·4, 26·8, 64·0 and 128 g/d), (cheese: 0·0, 0·9, 3·6, 8·5 and 17·0 g/d) and (yogurt: 0·0, 4·9, 21·0, 47·0 and 98·0 g/d)).

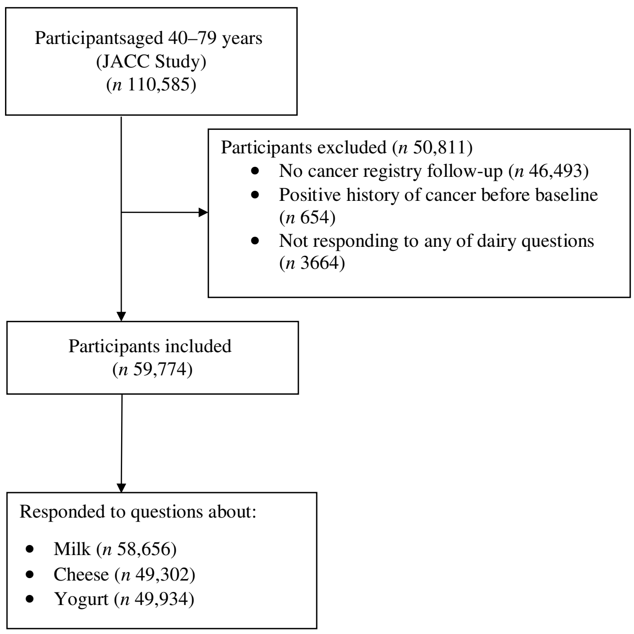

Fig. 1. Flow chart of the included participants in the JACC Study.

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On the other hand, the incident cases of PAC (outcome) were diagnosed per the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (C25). Cancer incidence was detected using population-based cancer registries supported by a systematic review of hospital-based cancer registries and inpatients' records of hospitals treating cancer patients[62].

Using the same baseline questionnaire, we collected data on participants' age, sex, weight, height, educational years, perceived stress, smoking and alcohol behaviours, leisure physical activity and walking, history of diabetes, family history of cancer and daily intakes of several foods that served in calculating daily energy intake (covariates).

Statistical analyses. The age and sex-adjusted *P*-value for significant differences in the participants' mean values and proportions of socio-demographic characteristics and common risk factors for PAC by their intake of different dairy products were calculated using the linear and logistic regression tests. The Cox proportional regression was used to compute the hazard ratios (HR) and their 95 % CI of the incidence of PAC for the intakes of milk, cheese and yogurt. To obtain statistical power, the two highest intake categories '*three to four times/week*' and '*almost every day*' were merged into one category '≥ *three times/week*'.

Person-years of follow-up were calculated from the date of responding to the JACC Study's baseline questionnaire to the date of PAC diagnosis, death, moving out or end of the study, whichever came first. The HR were adjusted for the following variables: age in years, sex (men and women), BMI (< 25 and ≥ 25 kg/m^2), educational years (< 18 and ≥ 18 years), perceived stress (no, mild, moderate and severe stress), smoking habits (never smokers, former smoker of < 20 cigarettes/d, former smoker of ≥ 20 cigarettes/d, current smoker of < 20 cigarettes/d and current smoker of ≥ 20 cigarettes/d), alcohol intake (never, former and current), leisure sports (never, one to two, three to four and ≥ five hours/week), walking (never, < 30, 30–60 and > 60 min/d), history of diabetes (yes and no), family history of cancer (yes and no) and quartiles of daily intakes of meat, vegetables and total energy (g/d). Besides, the possibility of interaction with sex, age, smoking and history of diabetes was examined. SAS version 9.4 software (SAS Institute Inc) was used for statistical analyses.

Ethical consideration. The research ethics committees of Nagoya University School of Medicine and Osaka University approved the protocol of the JACC Study. The study was conducted per the principles of the Declaration of Helsinki.

The meta-analysis

Literature search. First, we searched MEDLINE (PubMed), Embase and Web of Science for potential studies published in English before 31/3/2021 (the last day of data search) using the following terms: (Dairy OR Milk OR Cheese OR Yogurt) AND (Cancer). A full search strategy of PubMed was provided (online Supplementary file 1). Then, we conducted a manual search of the reference lists of retrieved articles and review articles to obtain additional studies. We reported this meta-analysis according to the checklist of PRISMA[65] and AMSTAR2[66].

Study selection. Studies were selected for analysis if they met the following criteria: (1) the exposure was milk, cheese or yogurt intake, (2) the outcome was PAC and (3) the study design was a prospective cohort. No limitations were set regarding the year of publication; however, no efforts were made to retrieve unpublished data. The following relevant information was extracted from the included studies: the last name of the first author, year of publication, study name, place of study, age and sex of participants, follow-up years, number of incident cases of PAC and covariates included in regression models. The multivariable-adjusted HR with 95 % CI of PAC according to the used categorisations for dairy product intake were also extracted (online Supplementary file 2). The quality of studies was determined using the modified Newcastle–Ottawa Scale based on studies' selection (representativeness, selection of the non-exposed, ascertainment of exposure and demonstration of the outcome), comparability and outcome (assessment, follow-up length and adequacy)[67].

Statistical analysis. We used the fixed-effects model to compute the pooled HR with 95 % CI of the included studies[68] because the test for heterogeneity was not significant according to the I^2 statistic, a measure of inconsistency across studies[69]. Publication bias was assessed using the regression test for funnel plot asymmetry[70]. All analyses were conducted separately on the following dairy products: milk, cheese and yogurt. To explore the impact of each study, we performed a sensitivity analysis by removing studies one by one and combining the remainders in separate analyses. R-3.2.0 statistical package (Metafor: A Meta-Analysis Package for R) was used for analysis[71].

Results

The Japan Collaborative Cohort Study

In the JACC Study, participants who reported the intakes of milk, cheese and yogurt were younger, with lower BMI, more educated, more physically active and more total energy consumers than their counterparts who reported no intake of the corresponding dairy products (Table 1).

Within a mean follow-up period of 13·0 years (median 13·4 years and maximum 21·6 years), a total of 198 incident cases of PAC were diagnosed. The consumption of the highest *v.* the lowest amounts of milk, cheese and yogurt was not associated with the risk of PAC in the age-and sex-adjusted regression models: HR (95 % CI): 0·91 (0·63, 1·33), 1·01 (0·58, 1·78) and 0·73 (0·41, 1·28), respectively. Adjustment for socio-demographic, clinical and nutritional variables did not change the results: HR (95 % CI): 0·91 (0·62, 1·33) for milk, 0·91 (0·51, 1·62) for cheese and 0·68 (0·38, 1·21) for yogurt. The *P*-values for trend across the increasing frequencies of the three dairy products were statistically insignificant. Also, the *P*-values for

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Table 1. Age-sex-adjusted socio-demographic characteristics of participants according to their dairy intakes of milk, cheese and yogurt (JACC Study) (Numbers; mean values and standard deviations)

	Never			1–2 times/month			1–2 times/week			≥ 3 times/week		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Milk												
Study population	10 491			4627			8065			35 473		
Age, years*		57·9	10·1		56·3	10·3		56·1	10·2		58·0	10·1
Men, %	44·4			47·8			41·8			38·3		
BMI, kg/m^2*		22·8	3·2		22·9	3·0		22·9	3·0		22·7	2·9
Education, years*		16·3	2·3		16·6	2·3		16·8	2·2		16·9	2·3
Perceived high stress, %	16·5			15·2			14·3			15·5		
Current smoking, %	30·1			30·3			25·9			19·6		
Current drinking, %	42·2			48·8			44·0			41·7		
No leisure sport, %	70·1			66·6			65·7			62·9		
No walking, %	9·7			8·5			8·8			9·0		
History of diabetes, %	3·9			4·2			3·8			5·8		
Vegetable intake, g/d		239·2	307·5		211·9	292·0		236·5	301·5		301·9	330·1
Meat intake, g/d		25·6	20·0		26·4	18·8		29·2	19·4		31·0	20·6
Energy intake, kcal/d*		1450·4	451·5		1478·4	455·5		1495·3	439·7		1561·9	416·9
Family history of cancer, %	7·2			7·5			5·3			5·6		
Cheese												
Study population	25 318			13 255			7007			3722		
Age, years*		58·0	10·0		54·7	9·7		55·5	10·1		57·8	9·9
Men, %	39·4			43·6			41·3			38·6		
BMI, kg/m^2*		22·9	3·1		22·9	2·9		22·7	2·8		22·5	2·9
Education, years*		16·5	2·3		17·2	2·2		17·3	2·3		17·4	2·4
Perceived high stress, %	17·0			16·3			17·3			19·2		
Current smoking, %	23·5			24·8			22·6			21·1		
Current drinking, %	39·3			49·4			46·6			44·1		
No leisure sport, %	73·5			67·9			64·5			61·7		
No walking, %	10·2			8·6			8·3			7·8		
History of diabetes, %	5·2			4·5			4·0			4·9		
Vegetable intake, g/d		247·2	309·5		261·4	312·9		336·2	338·5		380·6	352·8
Meat intake, g/d		25·3	18·6		30·6	18·4		36·1	20·7		39·6	27·1
Energy intake, kcal/d*		1458·0	421·9		1549·5	422·9		1637·8	425·0		1720·9	455·9
Family history of cancer, %	5·1			3·5			3·1			2·3		
Yogurt												
Study population	28 615			9032			6555			5732		
Age, years*		57·1	9·9		55·5	10·1		56·0	10·4		58·5	10·1
Men, %	47·4			33·4			28·8			30·6		
BMI, kg/m^2*		22·7	3·0		22·8	2·9		22·7	2·9		22·6	2·9
Education, years*		16·5	2·3		17·1	2·3		17·2	2·3		17·1	2·4
Perceived high stress, %	14·0			12·7			13·1			15·3		
Current smoking, %	28·1			18·8			15·9			15·7		
Current drinking, %	46·5			41·9			37·1			37·8		
No leisure sport, %	67·2			62·7			61·8			59·8		
No walking, %	10·4			8·8			8·8			9·5		
History of diabetes, %	4·9			4·6			4·3			5·6		
Vegetable intake, g/d		246·8	308·9		265·2	314·4		318·6	333·4		365·8	349·4
Meat intake, g/d		27·3	19·4		30·3	19·1		33·4	20·6		34·2	24·5
Energy intake, kcal/d*		1519·8	446·4		1497·4	410·0		1513·6	20·6		1568·5	420·2
Family history of cancer, %	7·8			5·7			4·8			4·1		

* Mean (standard deviation).

sex, age, smoking and history of diabetes interactions in the three dairy products were > 0·10 (Table 2).

The meta-analysis

Herein, we combined our results, in a meta-analysis, with the results of the other prospective cohort studies assessing the associations between the intakes of dairy products and the risk of PAC. After omitting irrelevant and retrospective studies, a short-list of seven prospective cohort studies was obtained[53–59] before three studies in the list were excluded; two studies for publishing more recent results from the same data[53,54] and one study for defining the exposure as dairy intake as a whole, not as elements of dairy intake[55] (Fig. 2). Eventually, four studies were eligible for meta-analysis[56–59] which became five after adding the current JACC Study. Of the four added studies, one study was a pooling of fourteen cohorts from North America, Europe and Oceania[56], one study was conducted in Norway[57] and the remaining two studies were conducted in Japan[58,59]. Among the five studies included for this meta-analysis, the assessment of dairy products was distributed as follows: milk in five studies, cheese in two studies and yogurt in four studies. Except for one study that assessed PAC deaths[58], all studies assessed the risk of PAC incidence. Only one study conducted

Table 2. The associations between dairy intakes of milk, cheese and yogurt and the risk of pancreatic cancer (JACC Study)
(Hazard ratio and 95 % confidence intervals)

		1–2 times/month		1–2 times/week		≥ 3 times/week		
	Never	HR	95 % CI	HR	95 % CI	HR	95 % CI	$P_{for\ trend}$
Milk								
Person-years	135 000	60 683		108 155		459 864		
Total population	10 491	4627		8065		35 473		
Incident cases	37	19		22		113		
Model I	1	1·25	0·72, 2·18	0·83	0·49, 1·41	0·91	0·63, 1·33	0·294
Model II	1	1·22	0·70, 2·13	0·81	0·47, 1·37	0·91	0·62, 1·33	0·308
Cheese								
Person-years	327 950	182 921		98 716		50 613		–
Total population	25 318	13 255		7007		3722		–
Incident cases	90	29		26		14		–
Model I	1	0·70	0·46, 1·06	1·08	0·70, 1·68	1·01	0·58, 1·78	0·596
Model II	1	0·67	0·43, 1·02	1·00	0·64, 1·58	0·91	0·51, 1·62	0·770
Yogurt								
Person-years	367 641	116 267		84 128		71 809		–
Total population	28 615	9032		6555		5732		–
Incident cases	92	20		11		14		–
Model I	1	0·78	0·48, 1·27	0·57	0·30, 1·06	0·73	0·41, 1·28	0·179
Model II	1	0·76	0·47, 1·24	0·55	0·29, 1·03	0·68	0·38, 1·21	0·137

Model I: Adjusted for age and sex.
Model II: Adjusted further for BMI, education, perceived stress, smoking behaviour, alcohol, leisure sport, walking, history of diabetes, family history of cancer and total meat, vegetables and energy intake.
P-values for sex interaction (milk = 0·80, cheese = 0·85 and yogurt = 0·25).
P-values for age interaction (milk = 0·20, cheese = 0·94 and yogurt = 0·94).
P-values for smoking interaction (milk = 0·30, cheese = 0·11 and yogurt = 0·40).
P-values for history of diabetes interaction (milk = 0·44, cheese = 0·92 and yogurt = 0·42).

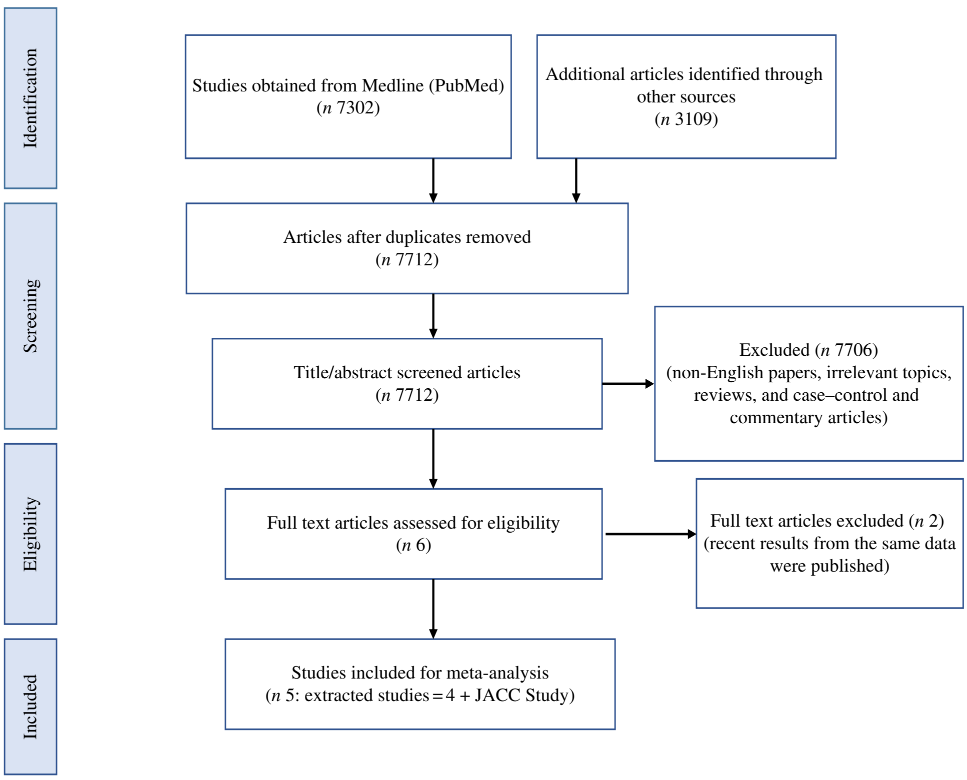

Fig. 2. Prisma chart of the included prospective cohort studies in the meta-analysis.

a sex-specific analysis[59] (Table 3). All studies, according to the modified NOS, were of good quality with scores ranging between seven and nine (online Supplementary file 3).

In agreement with the results of the JACC Study, the pooled HR (95 % CI) for milk, cheese and yogurt intakes in the meta-analysis showed no association with the risk of PAC: 0·95

Table 3. Summary of the prospective cohort studies included in the meta-analysis and investigating the associations between dairy intake and the risk of pancreatic cancer

Study ID	Description	Country	Exposure (groups)	Cancer cases	Covariates
Genkinger (2014)	A pooling of ATBC, BCDDP, CNBSS, CPS-II, CTS, COSM, HPFS, IWHS, MCCS, NLCS, NYSC, NHS, PLCO and SMC. Men and women aged 15–107 years and followed up for a maximum of 7–20 years	USA, Canada, Finland, Sweden, the Netherlands, Australia	Whole milk, cheese, yogurt and ice cream (highest *v.* lowest amount intake)	2212 (Incidence)	Age, year of questionnaire return, sex, BMI, smoking, alcohol, diabetes and energy intake
Ursin (1990)	Men and women aged 35–74 years and followed up for a maximum of 11 years	Norway	Milk (≥ 2 glasses/d *v.* < 1 glass/d)	62 (Incidence)	Age, sex and residence
Matsumoto (2007)	JMS Men and women aged 18–90 years and followed up for an average of 9·2 years	Japan	Milk, yogurt and butter (every day *v.* not every day)	13 (Mortality)	Age and sex
Khan (2004)	Hokkaido Women aged ≥ 40 years and followed up for an average of 14·8 years	Japan	Milk, yogurt and butter or margarine (several times/week and every day *v.* never, several times/year and several times/month)	13 (Incidence)	Age, health status, health education, health screening and smoking
	Hokkaido Men aged ≥ 40 years and followed up for an average of 13·8 years			12 (Incidence)	Age and smoking
This study (2021)	JACC Men and women aged 40–79 years and followed up for an average of 12·8 years	Japan	Milk, cheese and yogurt (highest ≥ 3 times/week *v.* no intake)	198 (Incidence)	Age, sex, BMI, education, stress, smoking, alcohol, leisure physical activity, walking, diabetes, family history of cancer and intakes of meat, vegetable and energy

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

(0·82, 1·11), 1·16 (0·87, 1·55) and 0·91 (0·79, 1·05), respectively. The JACC Study contributed to 16·2 %, 24·6 % and 5·7 % of the meta-analyses' weights for milk, cheese and yogurt, respectively. The meta-analyses of the three dairy products showed no heterogeneity across studies (I^2 % = 0·00 each). No signs of publication bias were detected in milk and yogurt meta-analyses, while conducting the regression test for publication bias in the cheese meta-analysis was unsuitable due to including two studies only (Table 4) (online Supplementary file 4). Removing the JACC Study from the milk and yogurt meta-analyses did not substantially change the HR (95 % CI): 0·96 (0·81, 1·14) and 0·93 (0·80, 1·07), respectively. The sensitivity analyses by leaving out studies one by one and combining the remainders did not affect the conclusion (online Supplementary file 5).

Discussion

The JACC Study indicated that, within a mean follow-up period of 13·0 years (median 13·4 years), the intakes of milk, cheese and yogurt were not associated with the risk of PAC among middle-aged Japanese, and no dose–response associations were noticed. Combining the results of the JACC Study with those from other prospective cohort studies, in a meta-analysis, did not materially change the findings.

The World Cancer Research Fund and the American Institute of Cancer Research, based on limited evidence, labeled the possible association between consumption of dairy products and the risk of PAC as '*limited/non-conclusive*'. We could not find any association between consuming dairy products and the risk of PAC[72].

Of note, the JACC Study included numerous strengths such as investigating the relationship between consuming several dairy products and the risk of PAC among a large study population, excluding participants with a history of cancer, using a prospective cohort design and lengthy follow-up period, assessing dairy intake using a validated food frequency sheet and adjusting the results for most potential confounders. Still, the JACC Study carried some limitations that should be addressed. First, the number of incident cases of PAC was limited that it did not allow us to stratify the results by potential risk factors for PAC such as sex, age, smoking behaviour and history of diabetes. Yet, this limitation was partly solved by combining the results of the JACC Study with the results of the other four prospective cohort studies via a meta-analysis. Besides, formal interaction tests showed that age, sex, smoking and diabetes did not affect the associations. Second, we obtained no data about the histopathological classifications of PAC cases and their treatment protocols after diagnosis. Third, data on dairy consumption were collected more than 30 years ago. Although dairy consumption per capita in Japan has been increasing since then, the current consumption of dairy products in Japan is much lower than the recommended levels[73,74]. Fourth, it could be speculated that the variation in the PAC ascertainment time across areas because of their different termination times (1994–2009) might have affected the PAC incidence. Yet, the age-adjusted PAC incidence and attributed mortality did not significantly change during this

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Table 4. Meta-analysis showing hazard ratios (95 % confidence intervals), weights and heterogeneity and publication bias across studies investigating the association between the intakes of milk, cheese and yogurt and the risk of pancreatic cancer
(Hazard ratio and 95 % confidence intervals)

	Milk			Cheese			Yogurt		
Author	HR	95 % CI	Weight %	HR	95 % CI	Weight %	HR	95 % CI	Weight %
Genkinger	0·98	0·82, 1·18	71·09	1·26	0·91, 1·76	75·43	0·93	0·81, 1·08	92·43
Ursin	0·71	0·41, 1·25	7·58	–		–	–		
Matsumoto	0·97	0·33, 2·90	1·99	–		–	1·19	0·15, 9·10	0·45
Khan (Women)	1·20	0·40, 4·10	1·74	–		–	0·90	0·20, 3·90	0·87
Khan (Men)	1·40	0·40, 5·20	1·43	–		–	0·50	0·10, 4·20	0·55
This study	0·91	0·62, 1·33	16·17	0·91	0·51, 1·62	24·57	0·68	0·38, 1·21	5·70
Overall	0·95	0·82, 1·11	100·00	1·16	0·87, 1·55	100·00	0·91	0·79, 1·05	100·00
I^2 % (*P*-value for heterogeneity)	0·00	0·887		0·00	0·338		0·00	0·823	
Z (*P*-value for publication bias)	0·025	0·980		–			–0·643	0·520	

period[75]. Fifth, this study focused on investigating the intake of dietary products as a whole rather than their nutrients; however, the intakes of vitamin D and Ca were shown in previous studies to be not associated with the reduced risk of PAC[56,76,77].

In addition, our meta-analysis posed several strengths such as augmenting the number of incident PAC cases, limiting the inclusion criteria to prospective cohort studies that avoided the methodological limitations of previous case–control studies, including studies of good quality according to the modified Newcastle–Ottawa Scale, and showing no signs of heterogeneity across studies or publication bias.

However, this meta-analysis had some limitations. First, the JACC Study and Genkiger et al study[56] together contributed to most incident cases of PAC and weights of the meta-analyses that were limited by the small number of included studies especially in terms of cheese and yogurt. Second, since exposure was self-reported in all studies, the possibility of non-differential misclassification bias cannot be entirely excluded. Third, it could be argued that two included studies[57,58] did not adjust their results for smoking, a major risk factor for PAC[78]; however, both studies contributed to small fractions of the meta-analyses weights. Moreover, adjusting for smoking and other socio-demographic, clinical and nutritional factors in the JACC Study did not materially change the results. Fourth, the included studies used different categories for dairy consumption. For example, the highest consumption categories of milk, cheese and yogurt in the Genkiger *et al* study[56] were ≥ 500, ≥ 50 and ≥ 57 g/d compared with ≥ 64, ≥ 8·5 and ≥ 47 g/d in the JACC Study, respectively. In the previous Japanese studies, Matsumoto *et al.*[58] assessed the risk among everyday consumers *v.* not everyday consumers, while Khan *et al.*[59] compared consuming more than to equal or less than several times per month, and both studies, however, did not calculate the consumed amounts of dairy products. Lastly, our meta-analysis protocol was not *a priori* registered, although we performed the meta-analysis in a standard way.

In conclusion, consumption of milk, cheese and yogurt was found to be not associated with the risk of PAC among middle-aged Japanese in the JACC Study, and the results did not change in the meta-analyses of prospective cohort studies. Since consuming dairy products was shown to have no role in reducing the risk of PAC, identifying other modifiable risk factors for PAC is important to reduce its burden.

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The authors declare no conflict of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521004232

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