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Dietary lactose and galactose intakes are associated with a later onset of natural menopause among women in a Japanese community

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Abstract

Galactose and its metabolites, primarily derived from lactose, may have toxic effects on the ovary. We aimed to prospectively examine the associations of galactose and lactose intakes with the onset of natural menopause. The data of a population-based cohort study in a Japanese community (the Takayama study) initiated in 1992 were analysed, with follow-up data collected in 2002. Among the participants of the Takayama study, premenopausal women (*n* 3115) aged 35–56 years at baseline were included in this study. Dietary intake, including lactose and galactose was assessed only at baseline using a FFQ. The menopausal status and age at menopause were determined based on the participants' self-reports, and natural menopause was defined as the absence of menstruation for 12 months or more. Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95 % CI. A total of 1790 women experienced natural menopause within the 10-year follow-up. Lactose and galactose intakes were associated with a later onset of natural menopause after adjusting for potential confounding factors and the HR (95 % CI) for the highest *v.* lowest quartile were 0·80 (0·69, 0·92) (*P*-trend = 0·001) in lactose and 0·86 (0·74, 1·00) in galactose (*P*-trend = 0·036), respectively. High intakes of lactose and galactose were associated with a later onset of natural menopause. Despite the presumed ovotoxicity effects, lactose and galactose intakes at usual levels may not be deleterious to the ovarian aging process among Japanese community-dwelling women.

Keywords: **Lactose: Galactose: Menopause: Prospective studies: Asia**

Menopause is the final step of the ovarian aging process, and its timing is an important determinant of specific diseases in women[1,2]. Later menopause is protectively associated with cardiovascular disease[3] and osteoporosis[4]; however, it is associated with an increased risk of breast[5], endometrial[6] and ovarian cancer[7]. The changes that entail ovarian aging, such as loss of ovarian function and the subsequent decline in endogenous estrogens, can exert different effects on the risk of these diseases[3,8,9].

The ovary may have negative impacts from accumulated galactose and galactose metabolites that are produced when lactose is dissolved by lactase in the small intestine, although galactose is crucial as a source of energy and a structural element in complex molecules[10,11]. Galactose-1-phosphate uridyl transferase is one of the enzymes responsible to metabolise galactose and relatively abound in the ovary[10]. Women who lack galactose-1-phosphate uridyl transferase (known as classic galactosemia) or who have reduced galactose-1-phosphate uridyl transferase activity tend to prematurely develop ovarian failure and menopause[12,13]. Irrespective of the transferase activity, high galactose intake could promote menopause[14]. However, evidence on the impacts of galactose and lactose intakes on the onset of natural menopause among community-dwelling women is limited.

To date, only two epidemiologic studies have investigated the associations between galactose intake and the onset of natural menopause[15,16]. Despite the presumed ovotoxicity effects of galactose, high intake of lactose, the main dietary source of galactose, was associated with a later onset of natural menopause in the Nurses' Health Study[16]. By contrast, a cross-sectional study in Iran indicated that galactose and lactose intakes were associated with an elevated odds of early menopause (natural menopause occurring before the age of 45 years), although the estimates were not significant[15]. Caution is warranted that only women who experienced natural menopause were included in the study and the OR showed the extent of discrepancy in the distribution of women with early menopause and non-early menopause. In the present study, we used the data from a 10-year follow-up study conducted in a Japanese community to examine the associations of galactose and lactose intakes with the onset of natural menopause. Classic galactosemia rarely occurs in Japan (approximately 1 case per 0·9 million population), and age at natural menopause varies by country or

Abbreviations: OC, oral contraceptive.

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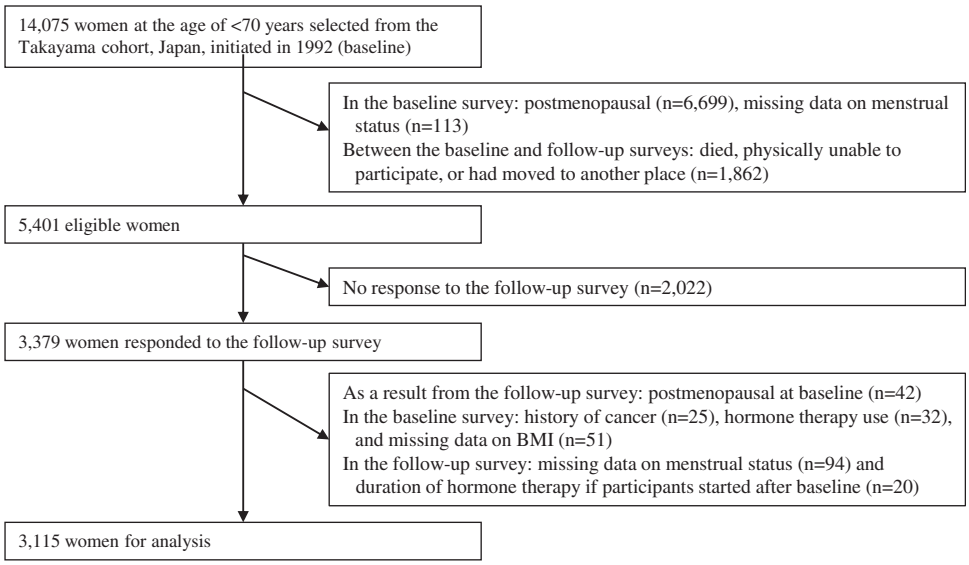

Fig. 1. Flow chart for selection of study participants from the baseline to follow-up surveys.

geographical region, for example, the mean age of 51·2 years in Australia, 50·1 year in Japan, 49·1 year in the USA, 47·4 years in the Middle East and 47·2 years in Latin America[9,17]. This study targeting Japanese community-dwelling women will aid in providing further insights into the associations.

Materials and methods

Study participants

Study participants for the present study were subjects of a population-based prospective cohort study initiated in September 1992, which targeted all residents aged 35 years or older in Takayama city, Gifu, Japan (the Takayama study). In total, 31 552 residents (85·3 %) completed a self-administered questionnaire, which included questions related to the participants' demographic characteristics, diet, lifestyle, reproductive health and medical histories. On July 1, 2002, a follow-up survey was conducted on participants aged < 70 years at baseline (12 471 men and 14 075 women). Details of the baseline and follow-up surveys were described previously[18]. For the present study, as shown in Fig. 1, 5401 premenopausal women were eligible after excluding those who were postmenopausal (*n* 6699) and had missing data on menstrual status (*n* 113) at baseline, and those who died, were physically unable to participate or had moved to another place between the dates of the baseline and follow-up surveys (*n* 1862). Among the eligible population, 3379 women responded to a self-administered questionnaire in the follow-up survey, which included questions about lifestyle, reproductive health and allergy and other medical histories (response rate: 62·5 %). We excluded women who previously diagnosed with cancer (*n* 25), used hormone therapy (*n* 32) and had missing data on body mass index (BMI) (*n* 51) at baseline. In the follow-up survey, those who were found to be already postmenopausal at baseline based on their responses to menstrual status (*n* 42) were excluded. Those who had missing data on menstrual status (*n* 94) and the duration of hormone therapy if they started after the baseline survey (*n* 20) were also excluded, leaving 3115 participants for analysis (35–56 years of age). The present study was approved by the Ethics Committee of Gifu University Graduate School of Medicine.

Natural menopause

The end point was the onset of natural menopause, which was defined as the absence of menstruation for 12 months or more. Data on self-reported menopausal status and age at menopause were obtained from the follow-up survey. Women were censored at the age when their menstrual period stopped due to surgery (*n* 129) and radiation therapy or chemotherapy (*n* 64). Since the timing of menopause for women on hormone therapy may not be accurate[19], those who reported to use hormone therapy in the follow-up survey were also censored at the starting age of hormone therapy (*n* 31).

Lactose and galactose intakes

Dietary intake was assessed at baseline using a validated 169-item semi-quantitative FFQ. The participants reported the frequency and amount of each food and beverage item they consumed during the past year. Component foods in dishes were determined in advance; a total of 520 foods were covered by the FFQ. Nutrient intake was estimated based on the frequency and portion size using the fifth revised and enlarged edition of the Japanese *Standard Tables of Food Composition*[20]. Details of the FFQ and the methods used for calculating nutrient intake were described previously[21]. We estimated the intake of each type of carbohydrate including galactose and lactose using an available carbohydrate table, that is, a supplement to the *Standard Tables of Food Composition, 2015* by the Japan Science and Technology Agency[22]. We examined the validity of the intakes of total energy, lactose and galactose estimated from the FFQ by comparing with the intakes from the twelve 1-d diet records obtained at 1-month intervals over 1 year in a

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subsample of participants. The Spearman's correlation coefficients were 0·51 (total energy), 0·71 (lactose) and 0·46 (galactose) in women.

Potential confounding factors

The following variables measured at baseline were considered as potential *a priori* confounders: i.e., age (continuous); age at menarche (≤ 12, 13–14, 15–16, or ≥ 17 years); age at first birth (≤ 25 or > 25 years); parity (0, 1 or 2, or > 2 children); oral contraceptive (OC) use (no or currently/ever); dietary intakes per day (total energy and total fat: continuous); BMI (quartile); height (quartile); physical activity (continuous); smoking status (never, former or current); marital status (married or not married [single, divorced/separated or widowed]) and years of education (≤ 11, 12–14, or ≥ 15 years). To reduce the possibility of multicollinearity[16], we combined the categories of age at first birth and parity into a single category: nulliparous, ≤ 25 years and 1 or 2 children, > 25 years and 1 or 2 children, ≤ 25 years and > 2 children or > 25 years and > 2 children. Physical activity was estimated based on the average hours per week spent performing various activities during the previous year. The time spent at a specific intensity level of activity was multiplied by its corresponding energy expenditure requirement, and all the intensity levels were summed to yield a score (metabolic equivalent [MET]-hour/week). Details of the method and its validity have been described elsewhere[23].

Statistical analysis

For each participant, person-years of follow-up was calculated from the time of the baseline survey (September 1992) to the onset of menopause, the end of follow-up (July 2002) or the time when a censoring event occurred, whichever came first. To evaluate the impact of non-response to the follow-up survey and exclusion because of missing data on menstrual status and hormone therapy, we first compared the baseline characteristics between respondents (eligible population) and participants for analysis. Then, we divided the participants into quartiles according to lactose and galactose intakes, respectively.

In the Cox proportional hazards models, we first estimated the hazard ratios and 95 % CI, after adjusting for age and total energy intake, for the associations of lactose and galactose intakes with the onset of natural menopause, using the first quartile category as the reference, respectively. Next, we additionally adjusted for other potential confounders: total fat intake, age at menarche, age at first birth and parity, OC use, BMI, height, physical activity level, smoking status, marital status and years of education. The dietary intakes (lactose, galactose and total fat) were adjusted for total energy intake using the residual method of energy adjustment[24]; the median value of each category of lactose and galactose intakes were entered into the models to analyse the linear trends in the associations.

In the sensitivity analyses, to reduce the potential impacts of genetic galactose-1-phosphate uridyl transferase deficiency and lactose intolerance on the onset of natural menopause[12], we first estimated the fully adjusted hazard ratios and 95 % CI after excluding women who did not consume milk. Second, to consider the potential impacts on misclassification of menopausal status[16], we repeated the analyses excluding women with a history of OC use at baseline and those who used hormone therapy during follow-up. Third, to reduce the possibility of residual confounding from dietary factors other than total energy and dietary fat, we additionally adjusted for overall diet quality in the fully adjusted models. Adherence to the food guide provided by the Japanese Government (i.e. the Japanese Food Guide Spinning Top; continuous) was utilised as an indicator of overall diet quality[25]. Finally, women who perceived perimenopausal signs could be conscious about their health and consume more milk and dairy products[26]. We, therefore, repeated the analyses excluding women who experienced menopause within the first 2 years of follow-up. The proportional hazards assumption was examined using Schoenfeld residuals and visual inspection of log-log plots, with no violations detected. We conducted a complete case analysis and defined statistical significance as a two-sided P value of less than 0·05. Stata SE statistical software (version 16·1; StataCorp) was used for all analyses.

Results

The baseline characteristics of the eligible population and participants for analysis are shown in Supplemental Table 1. The participants for analysis were more likely to start menarche at an early age and were less likely to be current smokers and educated compared with the eligible population. No difference was observed in the lactose and galactose intakes between the eligible population and participants for analysis.

Table 1 shows the baseline characteristics of participants for analysis according to the categories of lactose and galactose intakes. The participants consumed far more lactose than galactose. Women with low intakes of lactose and galactose consumed more total energy and less total fat and were more likely to use OC and smoke currently. Moreover, those with low intake of lactose were more likely to be married and were less likely to be nulliparous and educated.

Table 2 shows the associations of lactose and galactose intakes with natural menopause. During the 10-year follow-up (21 122 total person-years), 1790 women (57·5 %) had natural menopause. High intakes of lactose and galactose were associated with a later onset of natural menopause after adjusting for age and total energy intake. The associations remained significant even after adjusting for all potential confounding factors. Compared with the first quartile category, the fully adjusted hazard ratios (95 % CI) for the onset of natural menopause were 0·96 (0·83, 1·10), 0·87 (0·75, 1·01) and 0·80 (0·69, 0·92) from the second to forth quartile categories of lactose intake, respectively (P-trend = 0·001).

In the sensitivity analyses (Table 3), excluding women who did not consume milk, with a history of OC use, or who used hormone therapy during follow-up did not substantially change the present findings. Additionally adjusting for overall diet quality did not substantially change the results. Furthermore, the results after excluding cases within the first 2 years of follow-up remained consistent with those from the main analyses, although

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Table 1. Characteristics of study participants according to lactose and galactose intakes, Takayama study, Japan, 1992–2002
(Number and percentages; mean values and standard deviations)

	Lactose									Galactose								
	Q1		Q2		Q3		Q4		*P* value	Q1		Q2		Q3		Q4		*P* value
	n	%	*n*	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	*n*	%	
Intake range, g/d	< 5·0		5·0–< 8·4		8·4–< 12·4		≥ 12·4			< 0·17		0·17–< 0·29		0·29–< 0·42		≥ 0·42		
n	779		779		779		778			779		779		779		778		
Age																		
Mean	43·3		42·8		43·0		43·0		0·304	43·0		42·7		42·8		43·6		0·005
SD	4·4		4·3		4·6		4·6			4·5		4·4		4·4		4·6		
Total energy intake, kJ/d																		
Mean	607.6		481.6		486.6		524.9		<0·001	653.9		480.9		432.4		533.2		<0·001
SD	179.7		158.2		152.2		183.1			162.0		111.9		150.1		188.8		
Total fat intake, g/d (SD)																		
Mean	54·6		58·7		60·0		63·8		<0·001	56·0		58·8		61·0		61·3		<0·001
SD	13·0		10·2		9·1		10·0			13·4		10·4		8·9		10·7		
Age at menarche, *n* (%)																		
≤ 12 years	171	22·0	212	27·2	183	23·5	210	27·1	0·001	175	22·5	209	26·8	202	25·9	190	24·5	0·831
13–14 years	400	51·4	416	53·4	448	57·5	403	51·9		431	55·3	407	52·3	413	53·0	416	53·6	
15–16 years	189	24·3	135	17·3	141	18·1	148	19·1		158	20·3	151	19·4	150	19·3	154	19·9	
≥ 17 years	19	2·4	16	2·1	7	0·9	15	1·9		15	1·9	12	1·5	14	1·8	16	2·1	
Age at first birth and parity, *n* (%)																		
Nulliparous	37	4·8	38	5·0	41	5·3	69	9·0	0·001	35	4·6	35	4·6	47	6·1	68	8·9	0·001
≤ 25 years and 1 or 2 children	305	39·5	305	39·9	283	36·9	275	36·0		273	35·5	289	37·8	312	40·8	294	38·3	
≤ 25 years and > 2 children	189	24·5	151	19·8	153	19·9	158	20·7		191	24·8	170	22·2	133	17·4	157	20·4	
> 25 years and 1 or 2 children	171	22·2	192	25·1	219	28·5	203	26·6		190	24·7	197	25·8	206	26·9	192	25·0	
> 25 years and > 2 children	70	9·1	78	10·2	72	9·4	59	7·7		81	10·5	74	9·7	67	8·8	57	7·4	
Oral contraceptive use, *n* (%)	70	9·0	67	8·7	50	6·5	60	7·9	0·251	77	10·0	61	8·0	50	6·5	59	7·7	0·083
BMI, kg/m^2																		
Mean	22·1		21·9		21·9		21·9		0·192	22·2		21·8		22·0		21·9		0·073
SD	2·8		2·7		2·5		2·5			2·8		2·5		2·8		2·4		
Height, cm																		
Mean	154·9		155·0		154·7		155·2		0·397	154·9		155·2		154·8		154·9		0·449
SD	5·2		5·5		5·1		5·1			5·2		5·0		5·7		4·9		
Physical activity, MET-h/week (SD)																		
Mean	22·7		26·3		24·1		25·6		0·235	24·7		25·6		22·7		25·8		0·948
SD	29·9		35·9		31·9		35·2			32·6		33·7		31·4		35·6		
Smoking status, *n* (%)																		
Never	606	77·8	644	82·8	656	84·3	663	85·2	0·003	628	80·7	645	82·9	644	82·7	652	83·8	0·743
Former	51	6·6	46	5·9	44	5·7	42	5·4		50	6·4	41	5·3	47	6·0	45	5·8	
Current	122	15·7	88	11·3	78	10·0	73	9·4		100	12·9	92	11·8	88	11·3	81	10·4	
Married, *n* (%)	715	92·3	718	92·3	710	91·9	687	88·4	0·017	707	91·2	726	93·3	707	91·2	690	89·0	0·031
Years of education, *n* (%)																		
< 11 years	333	42·9	255	32·8	246	31·7	234	30·1	<0·001	269	34·6	272	35·0	269	34·7	258	33·2	0·753
12–14 years	387	49·8	446	57·4	461	59·3	455	58·6		430	55·3	435	55·9	445	57·4	439	56·5	
≥ 15 years	57	7·3	76	9·8	70	9·0	88	11·3		78	10·0	71	9·1	62	8·0	80	10·3	

IQR, interquartile range; *n*, number; Q, quartile.
Values are means ± SD, or frequencies (percentages).
P values were based on linear regression analyses for continuous variables and chi-square tests for categorical variables.

Table 2. HR and 95 % CI for the onset of natural menopause according to lactose and galactose intakes, Takayama study, Japan, 1992–2002

	Intake category							
	Q1	Q2		Q3		Q4		*P* for trend
Lactose								
Person-years	5054	5449		5285		5334		
n of cases	485	450		429		426		
Age- and energy-adjusted HR (95 % CI)*	1 (ref.)	0·96	0·84, 1·10	0·91	0·80, 1·04	0·83	0·72, 0·94	0·003
Fully adjusted HR (95 % CI)†	1 (ref.)	0·96	0·83, 1·10	0·87	0·75, 1·01	0·80	0·69, 0·92	0·001
Galactose								
Person-years	5296	5361		5370		5095		
n of cases	456	421		435		478		
Age- and energy-adjusted HR (95 % CI)*	1 (ref.)	0·94	0·82, 1·09	0·97	0·83, 1·12	0·88	0·77, 1·01	0·058
Fully adjusted HR (95 % CI)†	1 (ref.)	0·95	0·82, 1·11	0·93	0·79, 1·10	0·86	0·74, 1·00	0·036

HR, hazard ratio; n, number; Q, quartile.
HR < 1 implies later menopause and HR > 1 implies earlier menopause.
* Age and total energy intake were adjusted for.
† Age, total energy intake, total fat intake, age at menarche, age at first birth and parity, oral contraceptive use, BMI, height, physical activity, smoking status, marital status and years of education were adjusted for.

Table 3. Sensitivity analyses of HR and 95 % CI for the onset of natural menopause according to lactose and galactose intakes, Takayama study, Japan, 1992–2002
(Hazard ratio and 95 % CI)

	Intake category						
	Q1	Q2		Q3		Q4	
		HR	95 % CI	HR	95 % CI	HR	95 % CI	*P* for trend
Lactose								
Excluding women who did not consume milk (*n* 2602)	1 (ref.)	0·87	0·75, 1·02	0·82	0·70, 0·96	0·74	0·64, 0·87	<0·001
Excluding women with a history of oral contraceptive use at baseline (*n* 2608)	1 (ref.)	0·98	0·84, 1·14	0·87	0·74, 1·01	0·77	0·66, 0·90	<0·001
Excluding women who used hormone therapy during follow-up (*n* 2693)	1 (ref.)	0·96	0·83, 1·10	0·85	0·73, 0·99	0·77	0·66, 0·90	<0·001
Excluding cases within the first 2 years of follow-up (*n* 2556)	1 (ref.)	0·97	0·83, 1·13	0·85	0·72, 1·00	0·77	0·65, 0·90	<0·001
Additionally adjusting for overall diet quality (*n* 2800)	1 (ref.)	0·95	0·83, 1·10	0·86	0·74, 1·00	0·79	0·68, 0·91	0·001
Galactose								
Excluding women who did not consume milk (*n* 2602)	1 (ref.)	1·02	0·87, 1·20	0·94	0·80, 1·12	0·87	0·74, 1·01	0·027
Excluding women with a history of oral contraceptive use at baseline (*n* 2608)	1 (ref.)	0·93	0·79, 1·09	0·93	0·78, 1·10	0·82	0·70, 0·95	0·007
Excluding women who used hormone therapy during follow-up (*n* 2693)	1 (ref.)	0·97	0·83, 1·14	0·94	0·79, 1·10	0·86	0·74, 1·00	0·037
Excluding cases within the first 2 years of follow-up (*n* 2556)	1 (ref.)	0·91	0·77, 1·07	0·87	0·73, 1·04	0·84	0·72, 0·99	0·054
Additionally adjusting for overall diet quality (*n* 2800)	1 (ref.)	0·94	0·81, 1·10	0·92	0·78, 1·08	0·85	0·74, 0·99	0·035

HR, hazard ratio; n, number; and Q, quartile.
HR < 1 implies later menopause and HR > 1 implies earlier menopause.
In all models, age, total energy intake, total fat intake, age at menarche, age at first birth and parity, oral contraceptive use, BMI, height, physical activity, smoking status, marital status and years of education were adjusted for.

the linear trend in the association of galactose intake turned out to be non-significant.

Discussion

We examined the associations of dietary lactose and galactose intakes with the onset of natural menopause using the data of premenopausal women who participated in a prospective cohort study in a Japanese community. High intakes of lactose and galactose were associated with a later onset of natural menopause, after adjusting for age, total energy intake and other potential confounding factors. The sensitivity analyses did not substantially change the findings.

Lactose and galactose intakes at usual levels may not be deleterious to the ovarian aging process. Lactose intake was not associated with infertility due to ovulatory dysfunction in the Nurses' Health Study II[27], although lactose intake slightly improved the fecundability in two preconception cohort studies in the USA and Canada[28]. In addition, high intakes of lactose and galactose may decrease the risk of decline in anti-Mullerian hormone level, a marker of ovarian reserve[29]. In rats, high galactose diets inhibited the development of ovarian follicles[30] and long-term exposure to high lactose diets had no harmful effects on the ovarian morphology or function, although body weights and serum progesterone concentrations decreased[31].

Compatible with our findings (participants aged 35–56 years), a previous study found that high lactose intake was associated with a later onset of natural menopause only among women aged < 51 years at the time of questionnaire return in the Nurses' Health Study (median age at natural menopause in

the cohort)[16]. This can be due to the fact that menopause had already occurred to an irreversible degree among older women.

Endogenous steroid hormones and growth factors in cow's milk, which is a major source of lactose, could have impact on the present findings. Epidemiologic studies have suggested that milk and dairy product intakes increase the plasma concentrations of estradiol and insulin-like growth factor-I[32–36]. In addition, high intakes of low-fat dairy and skim milk were associated with a later onset of natural menopause[16] or a reduced risk of early menopause[37]. The concentrations of hydrophilic conjugated estrogen metabolites (e.g. estrone sulfate) are higher in low-fat dairy products and skim milk than in high-fat dairy products[38]. In rats, decreased brain insulin-like growth factor-I signaling leads to the luteinising hormone surge, which is typically observed during the reproductive senescence[39]. The estradiol and insulin-like growth factor-I in milk and dairy products might extend the lifespan of the ovaries.

Furthermore, gut microbiota could mediate the associations of lactose and galactose intakes with the onset of natural menopause. Specifically, the lactic acid bacteria *Lactobacillus* and *Bifidobacterium* can utilise lactose, which is eventually decomposed into lactate, short-chain fatty acids (mainly acetate, propionate and butyrate) and gases (H_2, CO_2 and CH_4)[40,41]. Gut microbiota may contribute to modulation of the hypothalamic–pituitary–gonadal axis including the gonadotropin-releasing hormone, gonadotropins and sex steroids as its components, and dysregulation of the hypothalamic–pituitary–gonadal axis can have a negative effect on the metabolic and reproductive health, for example, polycystic ovary syndrome[42]. Compared with control rats, polycystic ovary syndrome rats treated with *Lactobacillus* showed a reduction in androgen biosynthesis and an increase in granulosa layers with formation of corpora lutea in the ovarian tissues[43]. *Lactobacillus* are also colonised in the uterus[44]. Although the detailed mechanism is unclear, lactose and galactose intakes could help maintain healthy microbiota in the intestines and uterus, resulting in positive impacts on the ovarian aging process.

The present study has several limitations. First, the follow-up rate was low, and we could no longer obtain the data on menopausal status in women who died, were physically unable to participate, or had moved to another place. The participants for analysis were more likely to start menarche at an early age and were less likely to be current smokers and educated than the eligible population, although no difference was observed in the lactose and galactose intakes. In the present study, we adjusted for age at menarche, smoking status and years of education. Moreover, it is unlikely that women with high intakes of lactose and galactose tended to participate in the study if they reached menopause at a later age. Second, menopausal status and age at menopause are self-reported, which are of concern specifically in those who reached menopause at the beginning of the 10-year follow-up. Recall of age at menopause may not be affected by lactose and galactose intakes, but information about menopausal status and its timing should be collected repeatedly during the follow-up period, for example, biennially in the Nurses' Health Study[16,37]. Third, although women with a history of OC use at baseline were excluded in the sensitivity analyses, the possibility of residual confounding from OC use cannot be ruled out because the data on OC use was not collected in the follow-up survey. Fourth, dietary intake was assessed only at baseline and might change during the follow-up period specifically in women who perceived perimenopausal signs[26]. The sensitivity analyses excluding women who reached menopause within the first 2 years of follow-up did not substantially change the present findings. Finally, as mentioned above, we cannot rule out the possibility that the observed associations might be due to confounding by the unmeasured factors, including genes, hormones and nutrients in milk and dairy products.

Conclusion

In conclusion, high intakes of lactose and galactose were associated with a later onset of natural menopause. Despite the presumed ovotoxicity effects of galactose, lactose and galactose intakes at usual levels may not exert deleterious effects on the ovarian aging process among Japanese community-dwelling women. The timing of menopause is an important determinant of future disease risk in women. Age at natural menopause varies by country[9]. Hence, further studies in women from different countries are needed, and the associations of dietary lactose and galactose intake with the onset of natural menopause, considering microbiota in the intestines and uterus, genes and hormones and nutrients in milk and dairy products, should be examined.

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M. Y., K. W. and C. N. designed the study and analytical strategy; K. W. and C. N. obtained data; M. Y., Y. N. and C. N. performed analysis and interpreted data; M. Y. drafted the initial manuscript; K. W., Y. N. and C. N. reviewed and revised the manuscript; C. N. obtained the grant and supervised the study; and all authors read and approved the final manuscript as submitted.

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