Lactose intolerance and risk of lung, breast and ovarian cancers: aetiological clues from a population-based study in Sweden

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Background: Individuals with lactose intolerance are recommended to avoid milk or dairy products, which may affect the development of cancer.

Methods: We identified individuals with lactose intolerance from several Swedish Registers linked to the Swedish Cancer Registry to calculate standardised incidence ratios (SIRs) for cancers in the breast, lung, and ovary.

Results: A total of 22 788 individuals with lactose intolerance were identified, and their risks of lung (SIR = 0.55), breast (SIR = 0.79), and ovarian (SIR = 0.61) cancers were significantly decreased. Cancer incidences in the siblings and parents of individuals with lactose intolerance were similar to those in the general population.

Conclusions: In this large cohort study, people with lactose intolerance, characterised by low consumption of milk and other dairy products, had decreased risks of lung, breast, and ovarian cancers, but the decreased risks were not found in their family members, suggesting that the protective effects against these cancers may be related to their specific dietary pattern.

Lactose intolerance is a pathological condition characterised by abdominal symptoms caused by lactase deficiency (Vesa et al, 2000; Wilt et al, 2010). Lactose intolerance is an autosomal recessive condition related to two polymorphisms in the MCM6 gene (Enattah et al, 2002). The lowest reported prevalence is 2% in Scandinavia, whereas the prevalence in South America, Africa, and Asia is around 50%, increasing to 100% in some Asian countries (Sahi, 1994). Lactose-intolerant individuals can consume small amount of dairy products (yoghurt and cheese), or use enzyme substitutes (Wilt et al, 2010), but they are usually recommended to avoid dairy products. Lactose intolerance should not be mixed up with lactose malabsorption that is not a pathological condition but a normal human phenotype.

A previous study that examined the per capita milk consumption among 27 countries found that it was positively associated with ovarian cancer risk (Cramer, 1989); however, subsequent epidemiological studies gave inconsistent results (Larsson et al, 2004; Genkinger et al, 2006; Larsson et al, 2006). In addition, the associations of dairy products with breast (Boyd et al, 1993; Missmer et al, 2002; Moorman and Terry, 2004; Dong et al, 2011) and lung cancers (Axelsson and Rylander, 2002) (Kubik et al, 2004; van der Pols et al, 2007) were also inconclusive. A recent review by the World Cancer Research Fund and American Institute of Cancer Research claimed no sufficient evidence to establish associations between dairy intake and breast cancer risk (World Cancer Research Fund, 2007). Measurement error may partly explain these inconclusive data because most studies defined dairy consumption using questionnaires. All the previous studies examined cancer risks among those with high consumption of dairy products, using those with low consumption as the reference group. Here, we examined this association by an alternative approach: determining whether low consumption of dairy products in individuals with lactose intolerance can protect against the development of these cancers. This study could be regarded as an application of Mendelian randomisation to epidemiology (Qi, 2009). In addition, we examined the risk of cancer in the

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first-degree relatives (siblings and parents) of individuals with lactose intolerance to exclude potential confounding factors, which cannot be measured.

METHODS

Individuals with lactose intolerance were identified from four Swedish Registers: the Primary Health Care Registers covering the counties of Skåne (1987–2010) and Stockholm (2001–2007) and the national Swedish Hospital Discharge Register (1987–2010) and Outpatient Register (2001–2010). The Primary Health Care Register in Region Skåne, PaSIS, contains data on all individuals (around 1.2 million) living in Skåne and who visited primary health care between 1987 and 2010. The Primary Health Care Register in Stockholm covers 75 primary health care centres for the period 2001–2007. The Swedish Hospital Discharge Register was founded in 1964–1965 by the National Board of Health and Welfare, and it has had complete nationwide coverage since 1987. The Outpatient Register contains data on all visits to outpatient clinics in Sweden since 2001. Individuals with lactose intolerance were identified according to the International Classification of Diseases (ICD-9 code 271D and ICD-10 code E73). Individuals with secondary lactose intolerance (ICD-10 code E731) were excluded from the study.

We further linked the individuals with lactose intolerance to the Swedish Cancer Registry to identify all incident cases of cancer during the study period. The Swedish Cancer Registry was founded in 1958 and has close to 100% coverage at the present time (Ji and Hemminki, 2007). All linkages were performed using individual national identification numbers, which were replaced with serial numbers in order to preserve anonymity. We identified the siblings and parents of individuals with lactose intolerance from the Swedish Multi-Generation Register (Ekbom, 2011), which contains data on the biological parents of index persons registered in Sweden since 1961 and born in or since 1932.

We calculated person-years at risk among individuals with lactose intolerance from the date of birth, immigration, or 1 January 1961, whichever came last, until the date of diagnosis of cancer, death, emigration, or the end of the study period (31 December 2010), whichever came first. Standardised incidence ratios (SIRs) were calculated as the ratio of the observed and expected number of cases (Breslow and Day, 1987; Rothman and Greenland, 1998). The expected number of cases was calculated by using the population incidence rate for all individuals without lactose intolerance. Standardised incidence ratios were standardised by 5-year age group, sex (male and female), 5-year time period, and country of birth (Sweden, other European countries, and other countries) (Esteve et al, 1994). When calculating the SIRs for breast and ovarian cancers, additional adjustments were made for number of offspring (zero, one, two, and three or more) and age at first childbirth (<25, 25–34, and 35+ years). Confidence intervals (95%) for the SIRs were calculated assuming a Poisson distribution, and were rounded to the nearest two decimals (Esteve et al, 1994). All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

In Table 1, we present the basic characteristics of individuals with lactose intolerance and their first-degree relatives. A total of 22 788 individuals were identified with lactose intolerance in Sweden between 1987 and 2010. More women than men had lactose intolerance and the median age at diagnosis was 12 years. Most of the individuals with lactose intolerance (85%) were born in

Table 1. Basic characteristics of individuals in Sweden with lactose intolerance and their first-degree relatives

	First-degree relatives					
	Lactose intolerance		Siblings		Parents	
	No.	%	No.	%	No.	%
Sex						
Male	9468	41.5	16 602	50.6	18 323	49.4
Female	13 320	58.5	16 214	49.4	18 783	50.6
Year of birth						
Before 1950	2445	10.7	1934	5.9	7523	20.3
1950–1959	1100	4.8	1349	4.1	6543	17.6
1960–1969	1327	5.8	1682	5.1	13 220	35.6
1970–1979	1726	7.6	2912	8.9	8774	23.6
1980–1989	3190	14.0	6666	20.3	1045	2.8
1990–1999	7687	33.7	10 520	32.1	1	0.0
2000–	5313	23.3	7753	23.6		
Country of birth						
Sweden	19 400	85.1	30 341	92.5	29 468	79.4
Other European countries	1142	5.0	810	2.5	3394	9.1
Other	2246	9.9	1665	5.1	4244	11.4
Number of offspring						
0	16 971	74.5	25 296	77.1	0	
1	1586	7.0	2185	6.7	3807	10.3
2	2455	10.8	3167	9.7	16 194	43.6
3+	1776	7.8	2168	6.6	17 105	46.1
Age at birth of first child (years)						
<25	2483	10.9	3368	10.3	14 068	37.9
25–34	2897	12.7	3707	11.3	20 290	54.7
35+	437	1.9	445	1.4	2748	7.4
All	22 788	100.0	32 816	100.0	37 106	100.0

Sweden, and around 25% of them had at least one offspring during the study period.

During the 484 572 person-years of follow-up, the risks of lung (SIR = 0.55), breast (SIR = 0.79), and ovarian (SIR = 0.61) cancers were statistically significantly decreased (Table 2). The risk of lung cancer was similar among men and women. In Table 3, we present the risk of lung, breast, and ovarian cancer among the siblings and parents of individuals with lactose intolerance. None of the cancer sites showed a significantly decreased or increased SIR.

DISCUSSION

In this population-based study, a total of 22 788 individuals were identified with lactose intolerance between 1987 and 2010. This is, to our knowledge, the first study to examine the association between lactose intolerance and lung, breast, and ovarian cancers. The main finding was that the risks of lung, breast, and ovarian cancers were significantly decreased among individuals with lactose intolerance, whereas the incidences in their siblings and parents were similar compared with the general population.

The significantly decreased risk of lung, breast, and ovarian cancers in lactose-intolerant individuals suggests that these associations could be due to the low consumption of lactose or lactose-containing products. Caloric restriction has been found to be associated with a lower incidence of breast and ovarian cancers (Mao, 2004; Michels and Ekbom, 2004; Schouten et al, 2011; Zagouri et al, 2012). In addition, milk and other dairy products can contain high amounts of fats, particularly saturated fat, and some growth factors, such as insulin-like growth factor I (IGF-I), and these dietary components have been suggested to be associated

Table 2. Cancer risk in patients with lactose intolerance by gender

	Male				Female				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Lung	11	**0.51**	0.25	0.92	16	**0.58**	0.33	0.94	27	**0.55**	0.36	0.80
Breast					118	**0.79**	0.65	0.94	118	**0.79**	0.65	0.94
Ovary					16	**0.61**	0.35	0.99	16	**0.61**	0.35	0.99
All cancer	235	0.95	0.84	1.08	499	0.96	0.88	1.05	734	0.96	0.89	1.03

Abbreviations: CI = confidence interval; O = observed number of cases; SIR = standardised incidence ratio. Bold type, 95% CI does not include 1.00.

Table 3. Cancer risk among siblings and parents of patients with lactose intolerance

	Sibling				Parent			
	O	SIR	95% CI		O	SIR	95% CI	
Lung	30	1.02	0.69	1.46	131	0.85	0.71	1.01
Breast	90	1.02	0.82	1.26	337	0.92	0.83	1.03
Ovary	13	0.91	0.48	1.56	47	0.88	0.65	1.17

Abbreviations: CI = confidence interval; O = observed number of cases; SIR = standardised incidence ratio.

with the development of various types of cancers (Yu and Rohan, 2000; Goodwin *et al*, 2002; Stattin *et al*, 2004; Leosdottir *et al*, 2005; Gennigens *et al*, 2006). Insulin-like growth factor I can promote tumour cell growth through low apoptosis, high cell proliferation, and angiogenesis (Khandwala *et al*, 2000), and it was reported that high concentrations of IGF-I are associated with a greater risk of breast cancer (Renehan *et al*, 2004, 2006). Previous studies have found that high consumption of milk is associated with plasma IGF-I concentrations (Holmes *et al*, 2002; Morimoto *et al*, 2005), suggesting that low consumption of milk and other dairy products among individuals with lactose intolerance may be associated with a lower risk of breast cancer. Furthermore, avoidance of milk may alter the human gut microbiome, which may affect the development of tumours (David *et al*, 2014). However, we cannot exclude the protective effects on the development of cancers of other dietary patters, such as a consumption of plant milk (Ollberding *et al*, 2012; Wada *et al*, 2013), including soy and rice milks, which are often consumed by individuals with lactose intolerance. Moreover, whether the genetic variants found in lactose-intolerant individuals could confound the expression of other genes through linkage disequilibrium warrants investigation.

An important strength of this study is that all the data were retrieved from Swedish Registers with high quality and coverage. A recent review suggested that the diagnostic accuracy in Swedish Hospital Registers is high with a positive predictive value ranging between 85 and 95% (Ludvigsson *et al*, 2011). In addition, the number of patients included is large enough to guarantee reliable risk estimates. The prospective study design and the completeness of the follow-up of patients are other major advantages of the present study. One limitation of this study is the lack of information on some individual-level risk factors, such as smoking, alcohol consumption, dietary habits, psychosocial factors, and sociocultural behaviours, as well as the lack of genetic or physiological testing on the diagnosis of lactose intolerance.

In summary, individuals with lactose intolerance had decreased risks of lung, breast, and ovarian cancers, which may be related to their specific dietary patterns, but the contributions from other confounding factors should not be neglected.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JJ, KS, and JS were responsible for the study concept and design. JS obtained funding. KS and JS acquired the data. JJ analysed and interpreted the data. JJ did the statistical analysis. JJ drafted the manuscript, and all authors revised it for important intellectual content. JS is the guarantor.

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