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Original article

Milk consumption and risk of twelve cancers: A large-scale observational and Mendelian randomisation study

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SUMMARY

Background & aims: Milk consumption is a modifiable lifestyle factor that has been associated with several cancer types in observational studies. Limited evidence exists regarding the causality of these relationships. Using a genetic variant (rs4988235) near the lactase gene (*LCT*) locus that proxies milk consumption, we conducted a comprehensive survey to assess potential causal relationships between milk consumption and 12 types of cancer.

Methods: Our analyses were conducted using white British participants of the UK Biobank (n = up to 255,196), the FinnGen cohort (up to 260,405), and available cancer consortia. We included cancers with previous evidence of an association with milk consumption in observational studies, as well as cancers common in both UK Biobank and FinnGen populations (>1000 cases). We evaluated phenotypic associations of milk intake and cancer incidence in the UK Biobank, and then used a Mendelian randomisation (MR) approach to assess causality in the UK Biobank, FinnGen consortium, and combined analyses incorporating additional consortia data for five cancers. In MR meta-analyses, case numbers for cancers of breast, ovary, uterus, cervix, prostate, bladder and urinary tract, colorectum, and lung ranged between 6000 and 148,000 cases, and between 780 and 1342 cases for cancers of the liver, mouth, stomach and diffuse large B-cell lymphoma.

Results: In observational analyses, milk consumption was associated with higher risk of bladder and urinary tract cancer (OR 1.23, 95% CI 1.03–1.47), but not with any other cancer. This association was not confirmed in the MR analysis, and genetically predicted milk consumption showed a significant association only with lower risk of colorectal cancer (0.89, 0.81–0.98 per additional 50 g/day). In the MR analyses conducted among individual cohorts, genetically predicted milk consumption provided evidence for an association with lower colorectal cancer in the FinnGen cohort (0.85, 0.74–0.97), and in the UK Biobank greater risk of female breast cancer (1.12, 1.03–1.23), and uterine cancer in pre-menopausal females (3.98, 1.48–10.7).

Conclusion: In a comprehensive survey of milk-cancer associations, we confirm of a protective role of milk consumption for colorectal cancer. Our analyses also provide some suggestion for higher risks of breast cancer and premenopausal uterine cancer, warranting further investigation.

1. Introduction

The consumption of milk, an important dietary constituent for nutrition, has been associated with the risk of several cancer types. Since milk intake represents a lifestyle factor amenable to modification, it is of wide public interest to ascertain whether milk drinking has any beneficial or adverse causal effects on the risk of cancer.

Recent umbrella reviews of observational studies have reported an inverse association of milk consumption with the risk of

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Abbreviations

BCAC	Breast Cancer Association Consortium
BMI	Body mass index
CI	Confidence interval
DLBCL	Diffuse large B-cell lymphoma
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Oestrogen receptor
ICD	International Classification of Diseases
ILCCO	International Lung Cancer Consortium
LCT	Lactase gene symbol
MR	Mendelian randomisation
OCAC	Ovarian Cancer Association Consortium
OR	Odds ratio
PRACTICAL	Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome
SNP	Single nucleotide polymorphism

colorectal cancer [1–3] and a positive association with the risk of prostate cancer [1,3]. However, for many cancers findings for an association with milk intake are inconsistent, and problems arising from variable study designs and in some cases, low methodological quality, was noted in an overview of meta-analyses and systematic reviews covering 14 different cancer sites [4]. For example, while meta-analyses have provided some evidence for association of milk consumption with a higher risk of ovarian cancer [5], many studies have reported no association [6–8] or milk type-dependent associations [9]. For bladder cancer, the most recent meta-analyses have reported either an association of milk consumption with a lower risk [10,11], no association [12], or milk-type dependent associations [13]. Inconsistent findings have also been reported for breast cancer [14–17]. Among rarer types of cancer, meta-analyses have suggested an association between milk consumption and a lower risk of oral and oropharyngeal cancers [18], higher risk of gastric cancer [19] and higher risk of the diffuse large B-cell lymphoma (DLBCL) subtype of non-Hodgkin's lymphoma [20]. Milk intake has also shown an association with higher liver cancer mortality [21].

Since observational studies are susceptible to unknown confounding and reverse causality, it is unclear whether many of the reported associations reflect causal effects of milk consumption. Mendelian randomisation (MR) is a technique that helps minimise these undesirable influences by using germline genetic variant(s) established at birth to proxy an exposure. Variation in the lactase gene locus (*LCT*) encoding an enzyme that helps digest the milk sugar, lactose, affects levels of milk intake and is used in epidemiological studies as a proxy for this exposure. So far MR studies have provided some evidence for a causal effect of milk consumption on lower colorectal cancer risk, and increased risk of prostate cancer [22], while for other types of cancer, evidence is either absent or remains to be investigated.

In this study we used phenotypic and genetic data to evaluate the observational and genetic relationships between milk intake and several types of cancer. We conducted the analyses using data from the UK Biobank, and for the MR analyses, also included information from the FinnGen study [23] and all available consortia meta-analyses. We included cancers with more than 1000 cases in both the UK Biobank and FinnGen cohort databases and also investigated some rarer cancers where previous meta-analyses of observational studies have suggested risk differences associated with milk consumption.

2. Participants and methods

2.1. UK Biobank

The UK Biobank is a longitudinal cohort of around half a million participants aged 37–73 years (99.5% between 40 and 69 years) at the recruitment between 2006 and 2010 [24]. Extensive phenotypic and genetic data were collected, applying touchscreen questionnaires, verbal interviews, physical measurements, and sample collections (blood, urine and saliva), with the data further enriched through linking to electronic health records including cancer registries. The UK Biobank analyses were restricted to unrelated white British participants that had either no history of cancer or whose first ever diagnosed cancer was one of the 12 cancer outcomes investigated in this study. For observational analyses, we excluded all cases of cancer diagnosed before the baseline survey ('prevalent cases'), and the sample population was restricted to those with complete milk intake and covariate information, after which up to 249,418 participants remained. For MR analyses we retained prevalent and incident cancer cases, and used data on up to 255,196 individuals with information for lactase persistence genetic variant rs4988235 (Supplementary Fig. 1). For female cancer analyses we stratified by menopausal status using information from the UK Biobank baseline assessment, classifying individuals based on the question "Have you had your menopause (periods stopped)", including only those who answered "yes" or "no". Participants who had had a hysterectomy or who were not sure/did not answer were excluded.

Information about the type of milk that was mainly consumed by the UK Biobank participants was collected using touchscreen questionnaire, with the responses categorised as "full cream", "semi-skimmed", "skimmed", "soya", "other type of milk", and "never/rarely have milk" [25]. Those who had consumed full cream, semi-skimmed or skimmed milk were classified as dairy milk drinkers while the remaining others were classed as non-dairy milk drinkers, as previously described [26]. All participants provided informed consent, and ethical approval for the UK Biobank was granted by the National Information Governance Board for Health and Social Care and North West Multicentre Research Ethics Committee (11/NW/0382). We conducted the present study under application 20,175.

2.2. Cancer diagnoses

We included as outcomes, seven sex unspecific cancers including cancers of the bladder and urinary tract (referred to as bladder cancer here, for simplicity), colorectum, liver, lung, mouth, stomach, and DLBCL; four female cancers including those of the breast, cervix, uterus, and ovary; and prostate cancer in men. For the UK Biobank cohort, we identified cancer cases using cancer data available until November 2020 (for England and Wales) and October 2015 (for Scotland data) through linkage to the national cancer registry, and additionally used self-reported and hospital-inpatient data to define the controls. We first mapped the ICD (International Classification of Diseases) codes to 'phecodes', representing classifications that are more closely aligned with diseases commonly cited in clinical practice and genomic studies [27]. Diagnostic information is presented in Supplementary Table 1. For UK Biobank participants with multiple cancer diagnoses, we included the first diagnosed cancer, based on the date of diagnosis. For observational analyses, incident cancer cases were those reported after the baseline assessment. As controls for observational and MR analyses of the UK Biobank we used participants with no report of any type of cancer based on self-report, cancer registry, or

hospital inpatient data, or benign or *in situ* tumour from the cancer registry.

2.3. Genotyping

We used the rs4988235 single nucleotide polymorphism (SNP) near the lactase gene (*LCT*) for instrumenting milk consumption. The variant has 'C'/'T' alleles, and the 'T' allele is linked with lactase persistence in European populations, with each additional 'T' allele associating with 17.1 g/day (95% confidence interval (CI) 10.6, 23.6) more milk consumption in a subsample (n = 12,722) of the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study [28]. The rs4988235 variant was extracted from the third release genome-wide UK Biobank data, and coded as 0, 1, or 2, as per the number of 'T' alleles.

2.4. FinnGen and consortia

For the MR analyses, we supplemented data with summary-based information available from FinnGen, and different independent genome-wide association consortia. The FinnGen project aims to collect genomic and digital healthcare data from 500,000 individuals aged 18 years and above, and brings together almost all Finnish biobanks, and different Finnish pharmaceutical and health sectors [23]. Variant-disease association-based summary results can be accessed from the FinnGen database, with the current version (release 6, data release date: January 24, 2022) providing summary results for 260,405 (147,061 female and 113,344 male) participants, over 16 million variants, and nearly 2800 disease endpoints [29]. We additionally used variant-based summary results from non-overlapping consortia where available from the MR-Base database [30], which was possible for cancers of the breast (from Breast Cancer Association Consortium (BCAC); 122,977 cases) [31], endometrium (O'Mara et al. genome-wide association study; 12,906 cases) [32], ovary (Ovarian Cancer Association Consortium (OCAC); 25,509 cases) [33], prostate (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium; 79,148 cases) [34], and lung (International Lung Cancer Consortium (ILCCO); 11,348 cases) [35].

2.5. Statistical analysis

Observational analyses were conducted using the UK Biobank using logistic regression to explore the association between dairy milk intake and different cancer outcomes in a model adjusted for basic confounders (age, sex, and assessment centre), socioeconomic factors (education, Townsend deprivation index and employment), lifestyle factors (physical activity, smoking, alcohol consumption, and body mass index), long-standing illness, and general health status (Supplementary Table 2). MR analyses were performed using the rs4988235-milk consumption estimates (in g/day) from the EPIC-InterAct study [36], and rs4988235-cancer outcomes estimates from the UK Biobank, FinnGen cohort, and corresponding cancer consortium where available, with the estimates from UK Biobank being from logistic regression after adjusting for age, sex, assessment centre, genotyping array, 40 principal components and birth location. The causal estimates were calculated using ratio of coefficients (rs4988235-cancer estimates/rs4988235-milk consumption) MR method [37]. We combined causal estimates from different sources (UK Biobank, FinnGen, and consortia) using a random-effect meta-analysis method to compute the pooled causal effect estimate for each cancer, and tested heterogeneity using the I^2 statistic [38]. In secondary analysis, we repeated the MR analyses of female-specific cancer types among pre- and postmenopausal females using data from the UK Biobank. In sensitivity analyses, we assessed associations of genetically proxied milk consumption with different oestrogen receptor subtypes of breast cancer (ER- or ER+) using summary data from BCAC [31]. All the analyses were conducted using R version 3.6.1 and used the 'TwoSampleMR' package [30] for applying the MR ratio method, and the 'metafor' package [39] for performing the meta-analyses.

3. Results

3.1. Association of LCT gene variant with milk intake

For the genetic analyses our study population consisted of 255,196 participants of the UK Biobank, of which 53.4% were female. Population characteristics by lactase persistence genotypes are shown in Table 1, with extended information in Supplementary Table 3. As expected, lactase persistence was associated with greater likelihood of being a dairy milk consumer. In addition, those with lactase persistence tended to have a higher BMI, be from more deprived areas, and have achieved a lower level of education. Lactase persistence did not differ by sex, age, employment status, or long-standing illness.

3.2. Phenotypic associations with cancer types

Findings from observational analyses after full adjustment for age, sex, assessment centre, socioeconomic and lifestyle factors, are presented in Table 2. Dairy milk consumption was associated with greater risk of cancer of the bladder (odds ratio (OR) 1.23, 95% CI 1.03−1.47). No other phenotypic associations were observed among the other cancer types.

3.3. Association of the LCT variant with cancer types

We next used the MR approach to evaluate effects of genetically proxied milk consumption on risk of the 12 cancer outcomes, using the UK Biobank, FinnGen cohort, and cancer consortia (available for breast (female), uterus, ovary, prostate, and lung cancers), and combined population meta-analyses for each cancer type (Fig. 1). Among individual cohorts, genetically predicted milk consumption showed significant associations with lower colorectal cancer in the FinnGen cohort (OR per 50 g higher milk intake per day: 0.85, 95% CI: 0.74−0.97), and higher breast cancer risk among women in the UK Biobank (1.12, 1.03−1.23). There was some indication for an association between milk intake and other cancers in individual cohorts, including positive estimates for DLBCL (1.45, 1.00−2.11) and lung cancer (1.21, 1.00−1.48) in the UK Biobank, and a negative estimate for ovarian cancer in the FinnGen population (0.78, 0.60−1.01).

Low to moderate heterogeneity was detected across cohorts included in the combined MR analyses for the tested cancer outcomes (all I^2<67.8%). In pooled analyses using a random-effects model, genetically predicted milk consumption was associated only with lower risk of colorectal cancer (0.89, 0.81−0.98). Evidence was inconclusive with respect to an association between milk intake and cancer of the mouth (0.75, 0.55−1.03) and with cancers of the uterus (1.08, 0.99−1.18) and breast (1.04, 0.98−1.11) in females.

For female cancers, which may be influenced by hormone levels, we also performed MR analyses in pre- and postmenopausal women in the UK Biobank cohort. This revealed an association of genetically proxied milk consumption with higher risk of cancer of the uterus among pre-menopausal females. For breast cancer, MR

Table 1
UK Biobank participants' characteristics by lactase persistent genotype.

	All *n* (%)	Lactase persistent genotype			
		CC	CT	TT	*P*-value
All	255,196	15,050 (24.8)	93,381 (34.4)	146,765 (40.8)	
Age					0.9
39–49 years	63,348 (24.8)	3706 (5.9)	23,096 (36.5)	36,546 (57.7)	
50–59 years	87,672 (34.4)	5163 (5.9)	32,117 (36.6)	50,392 (57.5)	
60–73 years	104,176 (40.8)	6181 (5.9)	38,168 (36.6)	59,827 (57.4)	
Sex					0.52
Female	136,166 (53.4)	8060 (5.9)	49,786 (36.6)	78,320 (57.5)	
Male	119,030 (46.6)	6990 (5.9)	43,595 (36.6)	68,445 (57.5)	
BMI					**2.0E−12**
Underweight, < 18.5 kg/m^2	1245 (0.5)	91 (7.3)	491 (39.4)	663 (53.2)	
Normal, (≥18.5 and <25) kg/m^2	83,477 (32.7)	5160 (6.2)	30,948 (37.1)	47,369 (56.7)	
Overweight, (≥25 and <30) kg/m^2	108,316 (42.4)	6235 (5.8)	39,613 (36.6)	62,468 (57.7)	
Obese, ≥ 30 kg/m^2	61,332 (24.0)	3523 (5.7)	22,014 (35.9)	35,795 (58.4)	
Missing	826 (0.3)	41 (5.0)	315 (38.1)	470 (56.9)	
Education					**1.4E−07**
None	41,053 (16.1)	2299 (5.6)	14,725 (35.9)	24,029 (58.5)	
NVQ/CSE/A levels	91,501 (35.9)	5352 (5.8)	33,578 (36.7)	52,571 (57.5)	
Degree/professional	120,567 (47.2)	7296 (6.0)	44,338 (36.8)	68,933 (57.2)	
Missing	2075 (0.8)	103 (5.0)	740 (35.7)	1232 (59.4)	
Townsend deprivation					**9.3E−04**
Less deprived (below the median)	135,064 (52.9)	8083 (6.0)	49,701 (36.8)	77,280 (57.2)	
More deprived (above the median)	119,808 (46.9)	6952 (5.8)	443,551 (36.4)	69,305 (57.8)	
Missing	324 (0.1)	15 (4.6)	129 (39.8)	180 (55.6)	
Dairy milk intake					**6.90E−08**
No	19,993 (7.8)	1407 (7.0)	7303 (36.5)	11,283 (56.4)	
Yes	235,077 (92.1)	13,629 (5.8)	86,033 (36.6)	135,415 (57.6)	
Missing	126 (0.1)	14 (11.1)	45 (35.7)	67 (53.2)	

P-value from likelihood ratio test from linear regression on lactase persistent genotypes (0, 1 and 2 T-alleles) against the characteristics with adjustment for age and sex. *P*-value below Bonferroni-adjusted threshold of 4.5×10^{-3} shown in bold.

Table 2
Phenotypic associations between dairy milk consumption and incidence of 12 cancers in the UK Biobank.

Cancer type	Cases	Controls	Odds ratio (95% CI)	*P*-value
Sex unspecific (females and males)				
Bladder	2270	246,031	1.23 (1.03–1.47)	**0.02**
Colorectal	3387	246,031	1.04 (0.91–1.18)	0.61
Diffuse large B-cell lymphoma	449	246,031	1.12 (0.77–1.63)	0.56
Liver	306	246,031	1.12 (0.71–1.74)	0.63
Lung	2144	246,031	1.05 (0.89–1.24)	0.58
Mouth	355	246,031	0.81 (0.56–1.16)	0.25
Stomach	369	246,031	1.26 (0.81–1.96)	0.31
Sex-specific (females)				
Breast	5799	131,639	0.98 (0.89–1.07)	0.62
Cervical	272	131,639	0.95 (0.64–1.42)	0.80
Ovarian	722	131,639	1.11 (0.85–1.45)	0.46
Uterine	797	131,639	1.23 (0.94–1.61)	0.13
Sex-specific (males)				
Prostate	6451	114,392	1.05 (0.95–1.18)	0.33

Estimates are from logistic regression analyses and reflect comparisons between dairy milk consumers vs. participants not using milk/consuming non-dairy milk. Models were adjusted for basic covariates (age, sex, and assessment centre) socio-economic factors (education, Townsend deprivation index and employment), life-style factors (physical activity, smoking, alcohol consumption, and body mass index), long-standing illness, and general health status. CI indicates confidence interval. $P < 0.05$ shown in bold.

showed association with higher risk in post-menopausal females, with a directionally consistent estimate for premenopausal breast cancer (Table 3). Having observed limited evidence of an adverse effect on breast cancer, in sensitivity analyses we assessed associations of genetically proxied milk with different oestrogen receptor (ER) subtypes of breast cancer (ER- or ER+) using BCAC consortia information. No association was observed for either breast cancer type (Supplementary Table 4 in Supporting Information).

4. Discussion

In this large-scale study we evaluated relationships between milk consumption and 12 cancer types that are either common or whose risk has previously been associated with milk consumption. We confirmed a protective association between genetically predicted milk consumption and lower risk of colorectal cancer, while some evidence for a potentially adverse association was seen for female breast cancer, and uterine cancer risk in premenopausal females, warranting further investigation. We did not find convincing evidence to support effects of milk consumption on risk of the other types of cancer investigated.

There is strong evidence from observational studies of an inverse association between milk intake and colorectal cancer risk [1–3,40], and our MR findings provide causal evidence for this association, adding weight to another MR study [22] by inclusion of a larger series of colorectal cancer cases. The inverse association of milk (and other dairy) intake with colorectal cancer risk has been attributed to its high calcium content, as dietary calcium intake is also inversely related to risk of this cancer [2,40–45]. There are several potential mechanisms by which calcium could be protective, including neutralisation of pro-carcinogenic effects of free fatty acids and bile acids, inhibition of mucosal cell proliferation and promotion of cell differentiation and apoptosis, suppression of oxidative DNA damage, and modulation of colorectal cancer-related cell signalling pathways [46–48]. Milk also contains other potentially chemoprotective agents such as conjugated linoleic acids, short chain fatty acid butyric acid [46,49], and lactoferrin [50]. Consumption of iron supplements and iron-rich foods such as red and processed meats are linked to higher risk of colorectal cancer, with the pro-oxidative effects of iron likely contributing to DNA damage [51,52]. Given that calcium [53–56] and certain milk proteins [57] interfere with dietary iron absorption, they could potentially be protective that way.

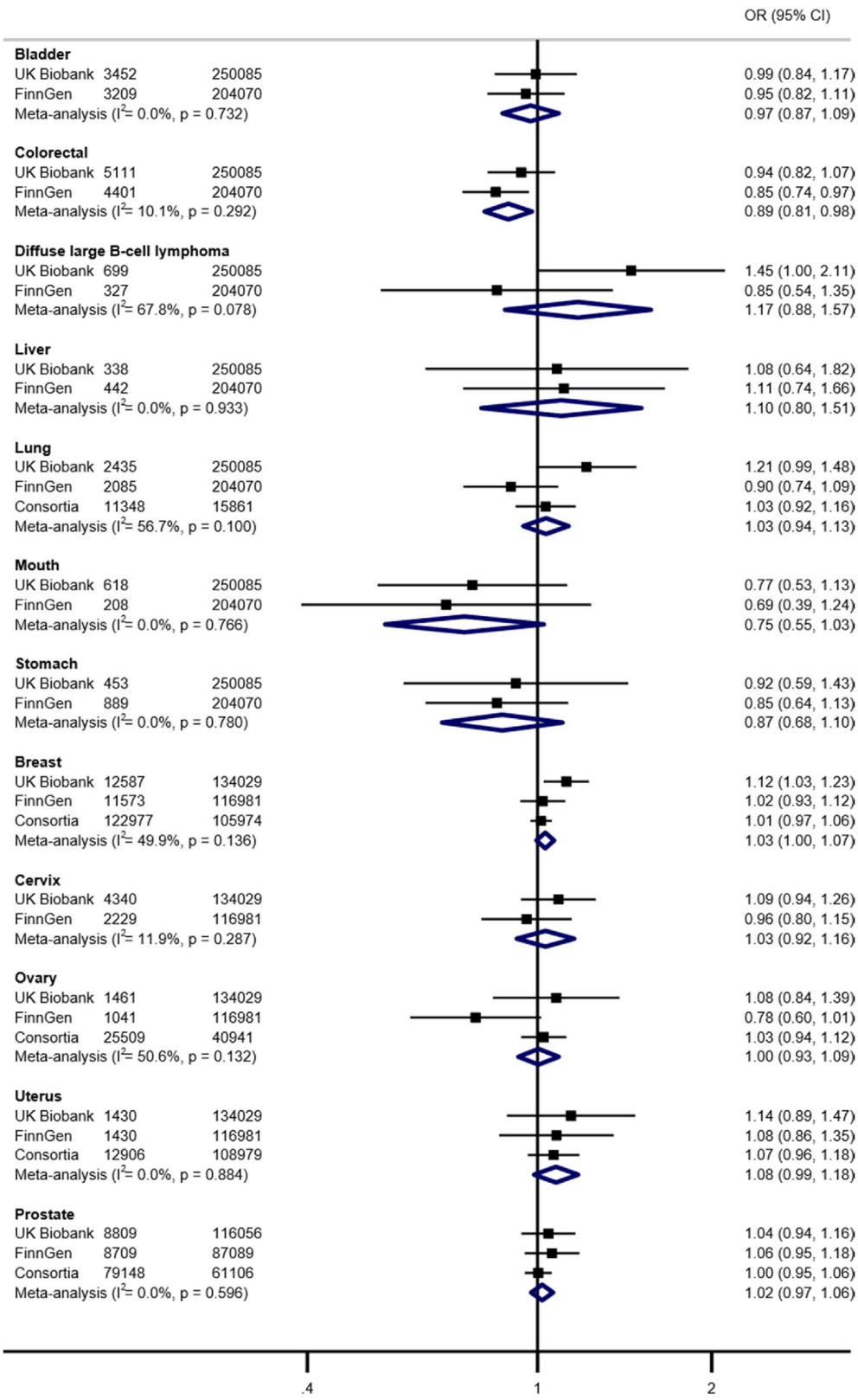

Fig. 1. Associations of higher genetically proxied milk consumption with 12 cancer types. Estimates are per (estimated) 50 g per day increase in milk consumption (1 milk intake-increasing allele of rs4988235 equates to approximately 17.1 g per day). OR indicates odds ratio, and 95% CI indicates 95% confidence interval. Consortia include BCAC [31], OCAC [33], PRACTICAL [34], and ILCCO [35] for cancers of the breast, ovary, prostate and lung, respectively, and a genome-wide association study cohort for cancer of the endometrium (uterus) [32].

Table 3
Associations of genetically predicted milk consumption and female cancers by menopausal status in the UK Biobank.

	Cases	Controls	Odds ratio (95% CI)	*P-value*
Breast				
Pre-menopause	1539	33,368	1.25 (0.97–1.60)	8.8×10^{-02}
Postmenopause	9100	79,714	1.14 (1.03–1.27)	$\mathbf{1.5 \times 10^{-02}}$
Cervix				
Pre-menopause	1329	33,368	1.07 (0.82–1.40)	6.2×10^{-01}
Post-menopause	2051	79,714	0.99 (0.80–1.23)	9.6×10^{-01}
Ovary				
Pre-menopause	170	33,368	0.90 (0.43–1.86)	7.7×10^{-01}
Postmenopause	957	79,714	1.23 (0.90–1.68)	2.0×10^{-01}
Uterus				
Pre-menopause	123	33,368	3.98 (1.48–10.7)	$\mathbf{6.2 \times 10^{-03}}$
Postmenopause	1106	79,714	1.00 (0.75–1.34)	9.8×10^{-01}

Estimates from the UK Biobank are from logistic regression after adjustment for age, sex, and assessment centre, genotyping array, 40 principal components and birth location. 95% CI indicates 95% confidence interval. $P < 0.05$ shown in bold.

Our study also uncovered a potential role for milk in increasing the risk of uterine cancer. It has previously been suggested that steroid hormones and growth factors such as oestrogens present in milk and dairy products may increase risk of uterine cancer among postmenopausal women; particularly those not receiving hormone replacement therapy [58]. However, our study suggests milk consumption may increase the risk of uterine cancer in pre-menopausal women only. A potential mechanism may be the menopause-delaying effects of milk consumption [59,60] since later menopause is a risk factor for uterine cancer [61]. Milk consumption also has an increasing effect on body mass index (BMI) [26] and strong evidence exists for a positive association between BMI and the risk of endometrial cancer (the most common uterine cancer) in premenopausal women [62].

We observed some evidence for an adverse effect of genetically proxied milk consumption on risk of female breast cancer in the UK Biobank population. These findings are, however, directionally opposed to findings from meta-analyses of observational studies which tend to link milk and dairy consumption to lower risk of breast cancer; particularly consumption of low fat or fermented dairy products [1,14,15,17,63,64], although not all studies have found conclusive associations [16]. While the reason for the adverse association in the UK Biobank MR analysis is unclear, it could be related to the type of milk products used, and commonly, lactose intolerant individuals can tolerate (and are recommended to use) fermented milk products [65].

A positive association was observed between dairy milk consumption and cancer of the bladder and urinary tract in our UK Biobank observational analysis but not in our MR analyses, consistent with previous MR studies [22,66]. Previously, findings from meta-analyses of observational studies have been inconsistent, showing either associations of milk consumption with lower risk of bladder cancer [10,11,13], no association [12,67], or milk type-dependent associations [13]. It cannot be excluded that reverse causality, or a confounding effect of kidney (dys)function, may influence the relationship between milk consumption and cancer of the bladder and urinary tract. For example, a lower glomerular filtration rate (a measure of poor kidney function) is associated with greater risk of renal and urothelial cancer [68] and is linked to lower retention of serum proteins. Endocrine signals of low protein states can drive protein appetite, and indeed, the hormone fibroblast growth factor 21, produced by the liver and muscle, signals protein deficiency and promotes a preference for protein-rich foods [69]. This kidney-protective hormone is emerging as an early marker of chronic kidney disease [70] raising the possibility that subclinical changes in kidney function could influence appetite for protein-rich dietary items such as milk. On the other hand, a low protein diet is often recommended for management of chronic kidney disease to reduce stress on the glomerulus [71]. Kidney function therefore has the potential to influence milk intake in different ways, which may underlie some of the inconsistences in the reported relationship between milk intake and risk of bladder-related cancers. Despite utilising large populations, we acknowledge that we were underpowered to confirm suggested milk associations with some of the rarer cancers (mouth, liver, stomach, DLBCL). However, a suggestive trend towards lower mouth cancer risk was seen in the UK Biobank phenotypic analysis, which is not inconsistent with previous observational studies linking milk intake with lower risk of oral and oropharyngeal cancers [18]. Also MR point estimates for cancer of the liver in the UK Biobank and FinnGen were directionally consistent with previous positive observations [21,72], warranting further studies with larger numbers of cases. Our analyses did not support a causal relationship with prostate cancer, in contrast to some limited MR evidence reported previously, using a smaller series of cases [22].

A strength of this study is the inclusion of a wide range of cancers, and unlike earlier investigations, we were able to look into all cancer types that have shown previous evidence of association with milk consumption in observational meta-analyses. The use of MR helps overcome some hurdles that complicate observational studies such as heterogeneity due to differences in measurements of milk intake across different studies, and reverse causality where symptoms or signs of cancer lead to a change in milk drinking habits. While we included some of the world's largest cohorts and supplemented information with consortia findings, we may have lacked power to detect an association for some cancers, in particular for those where consortia information was not available. In genetically instrumenting milk consumption with the lactase variant, we must acknowledge the possibility of pleiotropic effects. For example, the lactase persistence allele was associated with some demographic traits in our UK Biobank population, tending to be more common among individuals with lower education attainment and less common among individuals considered to be less deprived. The lactase persistence allele also associates with consumption of other dietary factors, and as such we cannot exclude the possibility of their effect on the outcome. For example, the milk-increasing allele has previously been found to associate with lower intake of fruits, non-alcoholic beverages, and wine [28], and it is feasible that lactose intolerant individuals that drink less milk compensate by supplementing their diet with better tolerated dairy products such as cheese and yoghurts, and consuming alternative beverages such as fruit juice or hot drinks. Milk drinking habits and tolerance are also associated with differences in BMI [26], and modulations in the microbiome [73], which may influence effects on the outcome. For analyses stratified by menopausal status, we acknowledge limitations such as not being able to confirm whether carcinogenesis started pre or post menopause, or to rule out an effect of milk consumption (or related factors) on the age of menopause. Finally, as we have limited our study to populations of European ancestry to reduce the possibility of population stratification biases such as differences in frequency of the lactase persistence allele, our observations may not be generalisable to other populations.

5. Conclusion

Our study provided additional support for a causal association between higher genetically predicted milk consumption and lower risk of colorectal cancer and some evidence of an increasing effect on female breast cancer and uterine cancer. No evidence of causality was observed for a variety of other cancer types, however several suggestive associations warrant further investigation.

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Author contribution

A.L. wrote the original draft and reviewed the literature. A.M. undertook the formal analyses and drafted the methodology. E.H. supervised the study, acquired funding and advised on analyses. All authors interpreted results, reviewed and edited the manuscript, and approved the final version for submission.

Data statement

All data and code from this study will be made available to approved users of the UK Biobank, upon application.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.11.006.

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