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The role of *MTNR1B* polymorphism on circadian rhythm-related cancer: A UK Biobank cohort study

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Abstract

A common *G* risk allele in the melatonin receptor 1B (*MTNR1B*, rs10830963) gene has been associated with altered melatonin signaling and secretion. Given that melatonin possesses anticancerogenic properties, we hypothesized that breast and prostate cancer risks vary by rs10830963 genotype. A total of 216 702 participants from the UK Biobank without cancer at baseline (aged 56.4 ± 8.0 years, 50.79% female) were included. Multivariable Cox regression adjusting for known risk factors for breast or prostate cancer was used to estimate the independent effects of the rs10830963 SNP and chronotype on cancer risk. Over a median follow-up of 8 years, 2367 (2.15% of women) incidences of breast cancer and 2866 (2.69% of men) incidences of prostate cancer were documented in females and males, respectively. rs10830963 genotype is not associated with cancer risk independently (female $P_{trend} = .103$, male $P_{trend} = .281$). A late chronotype is associated with breast cancer risk in females ($P_{trend} = .014$), but not prostate cancer risk in males ($P_{trend} = .915$). Further stratification analysis revealed that the rs10830963 genotype is associated with a breast cancer risk in females with moderate evening chronotype ($P_{trend} = .001$) and late chronotype is associated with breast cancer risk in females who carry rs10830963 G risk allele ($P_{trend} = .015$). Our study suggests that having a late chronotype might increase the risk of breast cancer among females, while the effect of *MTNR1B* rs10830963 genotype on breast cancer risk is mediated by chronotype.

KEYWORDS
chronotype, circadian rhythm, genetic risk of cancer, melatonin receptor 1B polymorphism, UK Biobank

What's new?

Circadian misalignment is closely related to the onset of hormone-dependent cancers, while melatonin exerts anticancerogenic properties. This is the first study to examine the potential interaction between a common G risk allele in the melatonin receptor 1B (MTNR1B, rs10830963) gene and an individual's chronotype on cancer risk. The findings suggest an effect

Abbreviations: BMI, body mass index; GWAS, genome-wide association studies; HRT, hormone replacement therapy; HWE, Hardy-Weinberg equilibrium; ICD, International Classification of Diseases; MAF, minor allele frequency; MT1, melatonin receptor 1; MT2, melatonin receptor 2; *MTNR1B*, melatonin receptor 1B; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome; SNP, single nucleotide polymorphism; T2D, type 2 diabetes.

of late chronotype on breast cancer risk that is stronger in rs10830963 G allele carriers. The rs10830963 G allele may only increase breast cancer risk among females with a late chronotype. These findings could help inform breast cancer risk estimation and direct new lifestyle interventions.

1 | INTRODUCTION

A growing body of evidence has shown that circadian misalignment, resulting from sleep deprivation, social jet lag or night shiftwork, is closely related to the onset of cancer,[1,2] especially hormone-dependent cancers such as breast cancer and prostate cancer.[3-6] Melatonin (*N*-acetyl-5-methoxytryptamine) is the primary endocrine signal that conveys the information of circadian rhythm from the brain to the peripheral tissues and cells.[7] The primary function of melatonin is to control the sleep-wake pattern and seasonality, and the dysregulation of circulating melatonin levels are usually associated with altered sleep behaviors.[8] Melatonin may also be involved in the regulation of many other physiological processes, including immune modulation, antioxidation, neuroprotection, antiaging, antiinflammation and endocrine regulation.[9] Thus, it has been gradually recognized that melatonin can also affect the initiation, development and treatment of cancer.[10] Epidemiological studies have observed that levels of circulating melatonin and its urinary metabolites are negatively associated with the risk of breast cancer.[11] Experiments in cell lines and animals have demonstrated the multidimensional anticancer effects of melatonin, including apoptosis induction, cell cycle arrest, metastasis inhibition and antiangiogenesis.[12,13] When being used in adjuvant settings of chemotherapy or radiation, melatonin has shown its potential to enhance the treatment efficacy, improve disease stability and ameliorate the radiochemotherapy-related side effects.[14,15]

The downstream effects of melatonin are mainly mediated by two high-affinity membrane receptors, melatonin receptor 1 (MT1, encoded by *MTNR1A*) and melatonin receptor 2 (MT2, encoded by *MTNR1B*).[16] rs10830963 single nucleotide polymorphism (SNP) is a common noncoding variation located in *MTNR1B*.[17] Studies have revealed that individuals who carry the G risk allele of rs10830963 exhibit an enhanced expression of MT2, as well as an altered melatonin secretion period per day.[18,19] Increased MT2 expression has been shown to lead to alterations in intracellular melatonin pathway in different cell types,[18,20] which may possibly serve as the driving force behind circadian rhythm disturbances and the pathogenesis of various diseases, including type 2 diabetes and myocardial infarction.[18,20,21] In addition, genome-wide association studies (GWAS) have identified the association between the rs10830963 G allele and the risk of diseases including polycystic ovary syndrome (PCOS)[22] and type 2 diabetes (T2D).[23] Despite a wealth of research on the common melatonin receptor SNP and cardiometabolic diseases, studies on the relationship between rs10830963 and cancer are scarce.

Usually determined by sleep timing, chronotype is the primary external manifestation of endogenous circadian rhythms. Having a late chronotype is known as a risk factor for cancer.[24,25] Moreover, the strength of the association between circadian-related genetic variants and diseases seems to be affected by a person's chronotype.[26] Given the crucial role of melatonin and its receptors in cancer development, as well as the important interplay between chronotype and altered melatonin profile on disease risks, it is necessary to investigate the association between the rs10830963 SNP, chronotype and the risks of prevalent circadian rhythm-related cancer in large cohorts.

In our study, we utilized data from UK Biobank, one of the largest population-based cohorts worldwide, and assessed the effect of rs10830963 SNP and chronotype on cancer risks separately. Given that prostate cancer and breast cancer are the most common type of cancer among men and women, respectively, and have the most evidence to date for their association with altered circulating melatonin rhythms and intracellular melatonin signaling pathways, we focused the present study on these two types of cancer, aimed to understand the role of rs10830963 SNP and chronotype in cancer, and elucidate whether and to what extent their effects might be mediated by each other.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study population

The UK Biobank is a large population-based prospective cohort that involves over 500 000 adults who were aged between 40 and 69 years and recruited from 22 assessment centers in the United Kingdom between 2006 and 2010.[27] At the baseline recruitment, participants completed a self-administered touchscreen questionnaire that included questions on sociodemographic information, medical history, family history of disease, lifestyle and environmental factors, employment status and sex-specific factors. Physical measurements including height, body weight, body composition and waist circumference were performed by trained personnel. Blood samples are collected and stored for genotype and biomarker assessment. Long-term follow-up was conducted through repeated measurement and the linkage to the electronic health record systems in the hospitals.

2.2 | Exclusion criteria

Data from the Initial UK Biobank Cohort including 502 466 participants whose genetic data passed quality control were utilized in the present study. The exclusion criteria were: (a) without *MTNR1B* rs10830963 SNP genotype data (n = 15 209); (b) were not used in genetic principal components (UK Biobank field ID 22020), to minimize the effect of relatedness (n = 80 162); (c) were not White British (n = 69 643), identified by self-reported ethnic background (ID 21000) and genetic ancestry based on the principal components analysis of the genotypes (ID 22006);

(d) had missing value in any of the covariates used in the analysis (n = 96 504). After these exclusions, a total of 240 948 White British individuals with variables of interest were available for further analysis.

Additional exclusions were made based on cancer diagnosis. The exclusion criteria were: (a) Participants with prevalent cancer at baseline (n = 22 691); (b) Subjects who had a breast or prostate cancer diagnosis as their secondary cancer (n = 308). The final analysis included 217 949 participants in total. The flow chart for the exclusions was presented in Figure S1.

2.3 | Genotype

Genome-wide genotyping was performed on all participants using the Affymetrix UK Biobank Lung Exome Evaluation (UK BiLEVE) Axiom array or the Applied Biosystems UK Biobank Axiom array.[28] Quality control was conducted, and over 96 million variants were imputed using the Haplotype Reference Consortium and the 1000 Genomes phase 3 dataset as reference panels. The Hardy-Weinberg equilibrium (HWE) testing was performed as previously reported and confirmed that the *MTNR1B* rs10830963 SNP did not deviate from the expected genotype proportion.[26]

2.4 | Chronotype

Chronotype (ID 1180) was self-reported based on the touchscreen questionnaire. The question was asked as "Do you consider yourself to be?" with six possible response options: "Definitely a 'morning' person," "More a 'morning' than 'evening' person," "More an 'evening' than a 'morning' person," "Definitely an 'evening' person," "Do not know" or "Prefer not to answer." Response of "Do not know" or "Prefer not to answer" were treated as a missing value. Response of "Definitely a 'morning' person," "More a 'morning' than 'evening' person," "More an 'evening' than a 'morning' person" and "Definitely an 'evening' person" were coded as "Extreme morning," "Moderate morning," "Moderate evening" and "Extreme evening," respectively. Responses to this question were consistent with the sleep timing objectively measured by the activity monitor.[29]

2.5 | Assessment of outcome

The cancer diagnosis was identified through linkage to national cancer registries and coded using the 10th Revision of International Classification of Diseases (ICD-10; ID 40006) or ICD-9 (ID 40013). Breast cancer was defined as registration in ICD-10:C50 Malignant neoplasm of breast or ICD-9:174 Malignant neoplasm of female breast. Prostate cancer was defined as registration in ICD-10:C61 Malignant neoplasm of prostate or ICD-9:185 Malignant neoplasm of prostate. Death record was identified through linkage to national death registries and defined by an empty record in date of death (ID 40000).

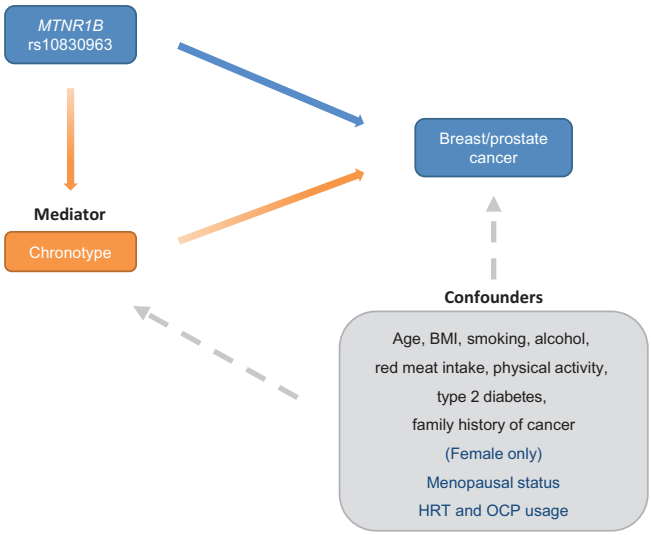

FIGURE 1 Simplified directed acyclic graph depicting the possible relationship between MTNR1B rs10830963 genotype, chronotype, breast and prostate cancer risks and confounders. BMI, body mass index; HRT, hormone replacement therapy; OCP, oral contraceptive pill [Color figure can be viewed at wileyonlinelibrary.com]

2.6 | Potential confounders

Important known risk factors for breast or prostate cancer were included as covariates in our analysis (Figure 1), including age at recruitment (ID 21022), body mass index (BMI) (ID 21001), smoking status (ID 20116, never/previous/current), alcohol intake frequency (ID 1558, daily or almost daily/three or four times a week/once or twice a week/one to three times a month/special occasions only/never), red meat intake (servings per week), physical activity (ID 22032, International Physical Activity Questionnaire activity group, low/moderate/high), family history of breast cancer or prostate cancer, respectively, and type 2 diabetes. Socioeconomic status (ID 189, Townsend deprivation index) and region of UK Biobank assessment center (ID 54, recoded into England, Scotland and Wales) was also adjusted. Genetic principal components of ancestry (ID 22009, first 10 columns) was adjusted when using rs10830963 genotype as an independent variable.

Red meat intake was derived from four variables, including processed meat intake (ID 1349), beef intake (ID 1369), lamb/mutton intake (ID 1379), pork intake (ID 1389). Frequency categories (never/less than once a week/once a week/times a week/five to six times a week/once or more daily) were recalculated into a continuous measure of red meat consumption per week. Family history of cancer was derived from three variables, including illnesses of father (ID 20107), illnesses of mother (ID 20110) and illnesses of siblings (ID 20111). Type 2 diabetes was identified if either of the two criteria was met: (a) T2D defined by a validated algorithm based on diagnosis, medication and self-reporting[30]; (b) HbA1c level ≥47 mmol/mol and was not defined as type 1 diabetes or gestational diabetes by the algorithm mentioned above. For the female population, we further controlled their menopausal status, the usage of hormone replacement therapy (HRT) and the usage of oral contraceptive pill (OCP). Menopausal

TABLE 1 Baseline characteristics of females in the UK Biobank population, stratified by gender

	Total	Female	Male	
	N = 216 702	N = 110 070	N = 106 632	*P*-value
Age, years	56.4 (8.0)	56.3 (8.0)	56.6 (8.1)	<.001
BMI, kg/m^2	27.3 (4.6)	26.8 (5.0)	27.8 (4.2)	<.001
Smoking status, n (%)				<.001
Never	118 643 (54.7%)	65 806 (59.8%)	52 837 (49.6%)	
Previous	76 711 (35.4%)	35 326 (32.1%)	41 385 (38.8%)	
Current	21 348 (9.9%)	8938 (8.1%)	12 410 (11.6%)	
Alcohol intake frequency, n (%)				<.001
Daily or almost daily	48 553 (22.4%)	19 577 (17.8%)	28 976 (27.2%)	
Three or four times a week	54 216 (25.0%)	24 728 (22.5%)	29 488 (27.7%)	
Once or twice a week	56 815 (26.2%)	29 198 (26.5%)	27 617 (25.9%)	
One to three times a month	23 379 (10.8%)	14 167 (12.9%)	9212 (8.6%)	
Special occasions only	20 762 (9.6%)	14 268 (13.0%)	6494 (6.1%)	
Never	12 977 (6.0%)	8132 (7.4%)	4845 (4.5%)	
Townsend index	−1.6 (2.9)	−1.7 (2.8)	−1.6 (2.9)	<.001
Region of test center, n (%)				<.001
England	191 088 (88.2%)	96 791 (87.9%)	94 297 (88.4%)	
Scotland	16 113 (7.4%)	8491 (7.7%)	7622 (7.1%)	
Wales	9501 (4.4%)	4788 (4.3%)	4713 (4.4%)	
IPAQ activity group, n (%)				<.001
Low	39 540 (18.2%)	19 774 (18.0%)	19 766 (18.5%)	
Moderate	88 938 (41.0%)	47 527 (43.2%)	41 411 (38.8%)	
High	88 224 (40.7%)	42 769 (38.9%)	45 455 (42.6%)	
Red meat consumption, servings/week	3.6 (2.2)	3.1 (1.9)	4.2 (2.3)	<.001
Menopausal status, n (%)				
Premenopausal	28 731 (26.1%)	28 731 (26.1%)		
Postmenopausal	61 540 (55.9%)	61 540 (55.9%)		
Had hysterectomy or bilateral oophorectomy	19 799 (18.0%)	19 799 (18.0%)		
Ever used hormone replacement therapy (HRT), n (%)	42 696 (38.8%)	42 696 (38.8%)		
Ever used oral contraceptive pill (OCP), n (%)	91 958 (83.5%)	91 958 (83.5%)		
Have family history of breast cancer, n (%)	23 222 (10.7%)	12 192 (11.1%)	11 030 (10.3%)	<.001
Have family history of prostate cancer, n (%)	17 391 (8.0%)	8830 (8.0%)	8561 (8.0%)	.96
Type 2 Diabetes, n (%)	10 262 (4.7%)	3310 (3.0%)	6952 (6.5%)	<.001
Chronotype, n (%)				<.001
Extreme morning	57 508 (26.5%)	29 874 (27.1%)	27 634 (25.9%)	
Moderate morning	79 443 (36.7%)	40 795 (37.1%)	38 648 (36.2%)	
Moderate evening	60 895 (28.1%)	30 357 (27.6%)	30 538 (28.6%)	
Extreme evening	18 856 (8.7%)	9044 (8.2%)	9812 (9.2%)	
MTNR1B rs10830963 genotype, n (%)				.069
C	114 029 (52.6%)	57 963 (52.7%)	56 066 (52.6%)	
CG/GC	86 055 (39.7%)	43 808 (39.8%)	42 247 (39.6%)	
GG	16 618 (7.7%)	8299 (7.5%)	8319 (7.8%)	

Note: Quantitative data are presented as mean ± SD. Qualitative data are presented as number (percentage).

status was classified into premenopausal, postmenopausal and had conducted bilateral oophorectomy or hysterectomy based on self-reported menopausal status (ID 2724, yes/no/not sure—had a hysterectomy), bilateral oophorectomy history (ID 2834, yes/no) and hysterectomy history (ID 3591, yes/no). HRT (ID 2814, yes/no) and OCP (ID 2784, yes/no) usage were defined by self-reported history.

TABLE 2 Hazard ratios and 95% confidence interval (CI) for breast cancer among females and prostate cancer among males, separated by rs10830963 genotype and chronotype

	Model 1			Model 2		
Exposure	**HR (95% CI)**	***P***	P_{trend}	**HR (95% CI)**	***P***	P_{trend}
Breast cancer incidence amount females						
rs10830963 genotype			.107			.103
CC	1			1		
CG	1.04 (0.96-1.14)	.317		1.05 (0.96-1.14)	.302	
GG	1.12 (0.97-1.31)	.130		1.12 (0.97-1.31)	.131	
Chronotype			.012			.014
Extreme morning	1			1		
Moderate morning	1.02 (0.91-1.13)	.774		1.02 (0.92-1.13)	.714	
Moderate evening	1.13 (1.01-1.26)	.029		1.13 (1.01-1.26)	.027	
Extreme evening	1.14 (0.98-1.34)	.091		1.14 (0.97-1.33)	.109	
Prostate cancer incidence amount males						
rs10830963 genotype			.223			.281
CC	1			1		
CG	0.95 (0.88-1.02)	.179		0.95 (0.88-1.03)	.187	
GG	0.96 (0.83-1.10)	.534		0.97 (0.84-1.12)	.664	
Chronotype			<.001			.915
Extreme morning	1			1		
Moderate morning	1.05 (0.96-1.15)	.284		1.07 (0.98-1.18)	.138	
Moderate evening	0.88 (0.79-0.97)	.011		1.01 (0.91-1.11)	.905	
Extreme evening	0.79 (0.68-0.92)	.002		1.03 (0.89-1.20)	.700	

Note: Model 1: Adjusted for the first 10 columns of the genetic principal components of ancestry for genotype; was not adjusted for any additional covariates for chronotype. Model 2 (breast cancer): Model 1 + adjusted for potential confounders including the region of UK Biobank assessment center, Townsend deprivation index, age at recruitment, BMI, smoking status, alcohol intake frequency, red meat intake, physical activity, type 2 diabetes, family history of breast cancer, menopausal status, usage of hormone replacement therapy and usage of oral contraceptive pills. Model 2 (prostate cancer): Model 1 + adjusted for potential confounders including the region of UK Biobank assessment center, Townsend deprivation index, age at recruitment, BMI, smoking status, alcohol intake frequency, red meat intake, physical activity, type 2 diabetes and family history of prostate cancer.
Abbreviations: CI, confidence interval; HR, hazard ratio.

2.7 | Statistical analysis

Cox proportional hazards regression was used to assess the associations of *MTNR1B* rs10830963 SNP and the risk of cancer, and the associations of chronotype and the risk of cancer. An additive genetic model was assumed for *MTNR1B* rs10830963 SNP. Analyses were performed separately for male and female. Time of follow-up was calculated from the date of attending UK Biobank assessment center (ID 53) until the date of cancer diagnosis (ID 40005), date of death (ID 40000) or the date of the last follow-up (14 December 2016), whichever came first. Participants who had a diagnosis of any cancer other than breast or prostate cancer, or had a death record during follow-up were censored from the analysis. The primary model (Model 1) for chronotype did not include any other covariates, while the primary model (Model 1) for *MTNR1B* rs10830963 SNP was adjusted for the first 10 genetic principal components of ancestry. The fully adjusted model (Model 2) additionally incorporated region of UK Biobank assessment center, Townsend deprivation index, age at recruitment, BMI, smoking status, alcohol intake frequency, red meat intake, physical activity, T2D, family history of breast cancer or prostate cancer. For female, menopausal status, HRT usage and OCP usage was also adjusted. The association between the interaction term "rs10830963 genotype * chronotype" and cancer risk was examined in both the primary and the fully adjusted models. Further stratification analysis for different genotype and chronotype groups was performed based on the interaction. All statistical analyses were performed using Stata software version 15.1 (StataCorp, College Station, Texas). A two-tailed $P < .05$ was regarded as statistically significant.

3 | RESULTS

The final cohort consisted of 50.79% females (n = 110 070) and 49.21% males (n = 106 632), with an average age at recruitment of 56.4 ± 8.0 years. General characteristics of the population stratified by gender are shown in Table 1. Genotype distribution of rs10830963

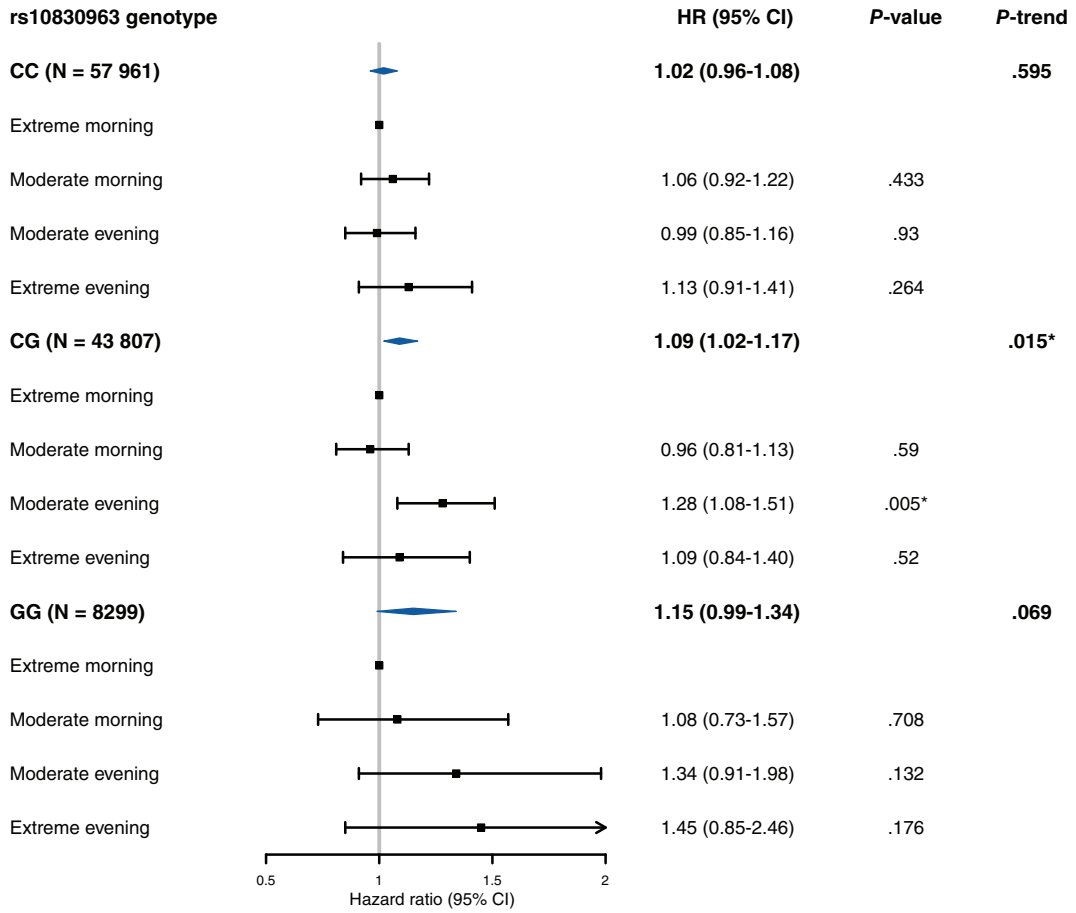

FIGURE 2 Fully adjusted hazard ratios and 95% confidence interval (CI) for the association between chronotype and breast cancer among females, stratified by the *MTNR1B* rs10830963 genotype. Adjusted for potential confounders including the region of UK Biobank assessment center, Townsend deprivation index, age at recruitment, BMI, smoking status, alcohol intake frequency, red meat intake, physical activity, type 2 diabetes, family history of breast cancer, menopausal status, usage of hormone replacement therapy and usage of oral contraceptive pills [Color figure can be viewed at wileyonlinelibrary.com]

in the whole population was 52.6% for CC, 39.7% for CG or GC and 7.7% for GG. The minor allele frequency (MAF) of the rs10830963 G allele was 27.5%.

Over a median follow-up of 8 years, 2367 (2.15%) incident cases of breast cancer were observed among females, and 2866 (2.69%) incident cases of prostate cancer were observed among males. Among the females, the number of G risk alleles did not predict the breast cancer risk during the observational period (1.05 [0.99-1.12], $P_{trend} = .103$; see Table 2 for pair-wise comparison using CC genotype as reference). Likewise, no linear trend was seen in the number of G risk alleles with prostate cancer among men (0.97 [0.91-1.03], $P_{trend} = .281$). Having a late chronotype significantly increased the risk of breast cancer in females (1.06 [1.01-1.10], $P_{trend} = .014$; see Table 2 for pair-wise comparison using Extreme morning chronotype as reference). For males, no association between chronotype and prostate cancer risk was detected (1.00 [0.96-1.04], $P_{trend} = .915$).

A significant interaction was found between rs10830963 genotype and chronotype regarding the risk of breast cancer (1.07 [1.00-1.15], $P = .049$). When we stratified the analysis in different genotype groups (Figure 2), we found that chronotype is associated with breast cancer risk only among females with genotype CG (1.09 [1.02-1.17], $P_{trend} = .015$), Females of GG genotype showed a similar trend (1.15 [0.99-1.34], $P_{trend} = .069$), but chronotype did not affect the risk of breast cancer among females with a CC (1.02 [0.96-1.08], $P_{trend} = .595$) genotype. Similarly, when we stratified the analysis in different chronotype groups (Figure 3), we found that having a G risk allele in *MTNR1B* rs10830963 is significantly associated with breast cancer risk only among females with a moderate evening chronotype (1.21 [1.08-1.36], $P_{trend} = .001$). No genotype-chronotype interaction regarding the risk of prostate cancer in males was found (1.01 [0.94-1.07], $P = .875$, stratification analysis see Figures S2 and S3).

4 | DISCUSSION

In the present study, we investigated the possible link between *MTNR1B* rs10830963 SNP, chronotype and the risk of breast and prostate cancers, and assessed the potential *MTNR1B* genotype-chronotype interaction on the cancer risk. Our findings do not suggest that *MTNR1B* rs10830963 is associated with an increased risk of breast or prostate cancer. To date, limited studies have been carried out regarding the association between *MTNR1B* rs10830963 SNP and

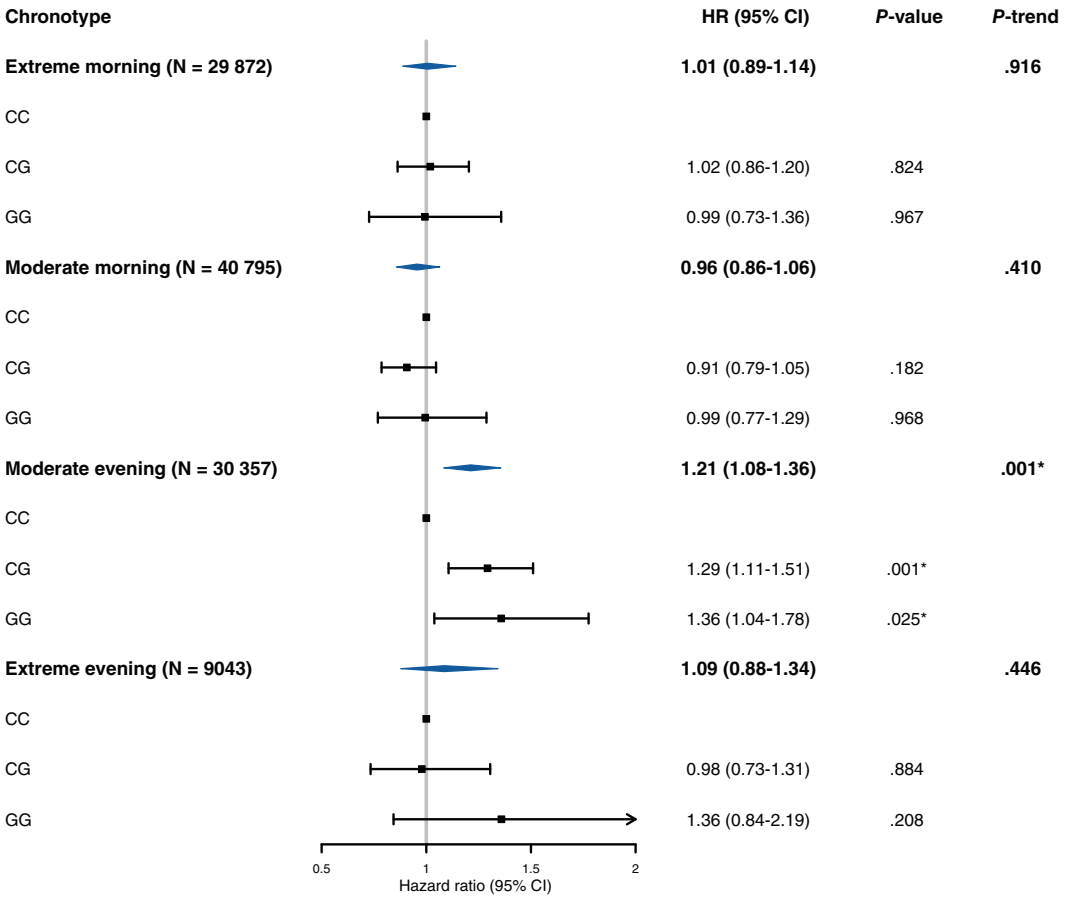

FIGURE 3 Fully adjusted hazard ratios and 95% confidence interval (CI) for the association between *MTNR1B* rs10830963 genotype and breast cancer among females, stratified by the chronotype. Adjusted for potential confounders including the first 10 columns of the genetic principal components of ancestry for genotype, region of UK Biobank assessment center, Townsend deprivation index, age at recruitment, BMI, smoking status, alcohol intake frequency, red meat intake, physical activity, type 2 diabetes, family history of breast cancer, menopausal status, usage of hormone replacement therapy and usage of oral contraceptive pills [Color figure can be viewed at wileyonlinelibrary.com]

breast cancer risk. A study among Chinese women in the Shanghai Breast Cancer Study[31] involving 2073 cases and 2083 controls suggested that rs10830963 SNP did not play a role in breast cancer risk, which is in line with our study. As for prostate cancer, a study involving 2782 cases and 4458 controls suggested that although *MTNR1B* rs10830963 SNP was nominally associated with the risk of prostate cancer, the significance did not persist after the adjustment for multiple comparisons.[32] Our finding is consistent with most of the existing evidence that the association between the *MTNR1B* rs10830963 SNP and cancer risk is not significant in the general population, and also in accordance with the previous GWAS where *MTNR1B* rs10830963 SNP has not been screened out as a risk factor for either breast cancer[33,34] or prostate cancer.[35,36]

Previous studies have consistently shown the association between negative health outcomes and poor sleep behaviors, including insomnia,[37] snoring,[38] inappropriate sleep duration[39] and late chronotype.[40] The underlying mechanisms might include circadian rhythm disruption, inflammation and associated behavioral risk factors such as poor diet intake and smoking. Chronotype refers to the activity-rest propensity of an individual during a 24-hour period. Mendelian randomization study showed that genetically proxied morning preference is protective for both breast cancer[24] and prostate cancer.[25] Our study using self-reported chronotype confirmed this association for the risk of breast cancer, but no significant results were found regarding the risk of prostate cancer. One possible explanation for this inconsistency could be the difference in the identification of chronotype. Our single-time questionnaire-based chronotype assessments could be subject to a certain degree of reporting bias. Nevertheless, we could still see a relatively strong tendency that late chronotype increases the risk of breast cancer in females.

To our knowledge, the present study is the first study that examines the potential interaction between *MTNR1B* rs10830963 genotype and chronotype on the risk of cancer. A significant association between the genotype-chronotype interaction and breast cancer risk in females was identified, and this further motivated us to stratify the analysis in different genotype and chronotype subgroups among females. We found that chronotype was associated with breast cancer risk among females with a CG genotype, while among females with a GG genotype, the significance level is marginal after adjusting all potential confounders. Likewise, the *MTNR1B* rs10830963 G allele

significantly increases the risk of females who report a moderate evening chronotype, while for females who report an extreme evening chronotype, the association did not reach a significant level. This could be because both people with a GG genotype in rs10830963 and people with an extreme evening chronotype are the minority group that only account for approximately 8% of the population, analysis in the subgroup that meets both criteria did not have enough statistical power. Taken together, our stratification analysis suggested that the effect of late chronotype on breast cancer risk is stronger in rs10830963 G allele carriers, and rs10830963 G allele might only increase the risk of breast cancer among females who have a later chronotype.

Several potential pathological pathways may account for the association between *MTNR1B* rs10830963 and breast cancer. For example, the G risk allele in rs10830963 is associated with impaired insulin secretion and increased fasting glucose levels,[23] and hyperglycemia can promote breast cancer progression directly.[41] Secondly, the G allele may alter the MT2 expression in breast tissues, leading to a change in the central circadian clock and peripheral oscillators, such as the expression of the clock genes period 1 (*Per1*) and period 2 (*Per2*), which are known tumor suppressor genes.[42] Previous studies have also demonstrated that the G risk allele in rs10830963 is associated with a later dim-light melatonin offset and a longer melatonin duration at night.[19] Melatonin is a crucial modulator of the estrogen-estrogen receptor α signaling pathway. Changes in the melatonin physiology might lead to changes in the inhibitory effect of melatonin on the estrogen-mediated proliferation of human breast cancer cells.[43]

Despite our extensive investigations conducted in a large cohort, several limitations apply to the present study. Primarily, information on the stage and grade of the tumor and the status of the hormone receptor is currently unavailable in the dataset. Thus, we could not investigate whether the associations we found would vary according to these clinical cancer characteristics. Secondly, as an observational epidemiological study, our results could not infer causality of *MTNR1B* rs10830963 SNP on breast cancer. Further case-control studies with prospectively collected confounding factors and more detailed measurements on the exposures are needed to draw a definite conclusion.

With the prevalence of circadian rhythm-related cancer on the rise, understanding the role of genetic factors such as the SNPs in the melatonin pathway genes is critical for developing novel prevention strategies. Our results in our study pointed out a potential interaction between chronotype and *MTNR1B* rs10830963 SNP on the risk of breast cancer, and supported a probable causal effect of rs10830963 GG genotype on breast cancer carcinogenesis among females with late chronotype. These findings might help inform current efforts on the risk estimation of breast cancer, and direct new avenues of tailored lifestyle intervention on an individual basis. This could ultimately help reduce the social and economic burden caused by circadian rhythm related cancers.

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CONFLICT OF INTEREST

The authors of this article have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Xiao Tan and Jiafei Wu designed the study. Jiafei Wu performed the statistical analysis and wrote the original draft. Xiao Tan supervised the analysis and the writing of the original draft. Both authors reviewed and approved the final version of the article submitted for publication. The work reported in the article has been performed by the authors, unless clearly specified in the text.

DATA AVAILABILITY STATEMENT

This research has been conducted using the UK Biobank resource under application number 43015. The UK Biobank is an open access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Ethical approval of the UK Biobank study was acquired from the North West Multi-centre Research Ethics Committee (MREC), and written informed consent was provided from all participants.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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