Association between polymorphism near the \textit{MC4R} gene and cancer risk
A meta-analysis

Tian Zeng, BS\textsuperscript{b}, Jing Zhao, MD\textsuperscript{a}, Yu Kang, BS\textsuperscript{b}, Xiaojiao Wang, MD\textsuperscript{b}, Hongjun Xie, MD\textsuperscript{a,*}

**Abstract**

Objectives: Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) near the melanocortin 4 receptor (MC4R), gene which are associated with risk of obesity. Since obesity is an established risk factor of cancer, several studies have examined the association between SNPs near the MC4R gene and cancer risk, but the findings are inconsistent. The present study aimed to perform a meta-analysis to clarify the association between SNPs near MC4R and cancer risk.

Methods: The PubMed and Embase databases were searched for potentially eligible publications. All studies that evaluated the association between MC4R rs17782313 SNP (or its proxy rs12970134) and cancer risk were included. The pooled odds ratios with 95% confidence intervals (CIs) were calculated using the random-effects model. And subgroup analysis by cancer type (colorectal cancer, endometrial cancer and breast cancer) was conducted for further investigation the association.

Results: A total of 6 eligible studies (6517 cases and 16,886 controls) were included in the present meta-analysis. The results indicated that MC4R rs17782313 SNP was moderately associated with cancer risk (odds ratio = 1.12, 95% CI = 1.01–1.24). However, the subgroup analysis between different cancer types shows that rs17782313 is only associated with colorectal cancer but not the endometrial cancer and breast cancer. Risk factor in colorectal cancer was both significantly associated with rs17782313 with and without adjustment for body mass index; while the risk factor of the endometrial cancer and breast cancer were both not associated with the rs17782313 with and without adjustment for body mass index. There was no publication bias for the association between MC4R rs17782313 and cancer risk.

Conclusion: The present meta-analysis confirmed the moderate association between MC4R rs17782313 and cancer risk.

Abbreviations: BMI = body mass index, CI = confidence interval, MC4R = melanocortin 4 receptor, OR = odds ratio, SNPs = single nucleotide polymorphisms.

Keywords: cancer, MC4R, meta-analysis, single nucleotide polymorphism

1. Introduction

In 2008, the genome-wide association studies (GWAS) reported that rs17782313 single nucleotide polymorphism (SNP) mapped 188 kb downstream of the melanocortin 4 receptor (MC4R) gene was strongly associated with body mass index (BMI) and risk of obesity in European populations.\cite{1} Furthermore, subsequent studies have confirmed the positive association between SNPs in/ near the MC4R gene and risk of obesity in populations with different races/ethnicities.\cite{2–4}

MC4R is a 332-amino acid protein encoded by a single exon on chromosome 18q22. The rare coding mutations in the MC4R gene have been found to be the main cause of human monogenic obesity,\cite{5} suggesting that the MC4R gene represents a compelling biological candidate. MC4R expression is also associated with risk of early-onset obesity, increased lean mass and bone mineral density, and enhanced linear growth.\cite{6} Two previous meta-analyses confirmed that the rs17782313 SNP near the MC4R gene was associated with risk of obesity\cite{8–10} and type-2 diabetes.\cite{11} It has been well-documented that obesity is the leading risk factor for many cancers. Therefore, it is important to determine whether MC4R SNPs are associated with cancer risk, which may help illuminate the potential biological mechanism between obesity and cancer development. To date, several studies have investigated the associations of MC4R SNPs with risk of cancer.\cite{12–14} However, the findings have been contradictory.

The present study aimed to perform a systematic meta-analysis to clarify the association between the rs17782313 SNP (or its proxy) near the MC4R gene and risk of cancer.

2. Materials and Methods

2.1. Literature and search strategy

The PubMed and Embase databases were searched for potentially eligible studies. The following key words were used to search for...
Publication bias was assessed by Begg test and Egger test\[17\] for BMI, as well as after adjusting for BMI (\(P_{\text{adj}} = .308 \text{ and .310}, P_{\text{adj}} = .308 \text{ and .310}, \text{respectively}).

### 3.2. Meta-analysis results

Before adjusting for BMI, the MC4R rs17782313 SNP risk allele was moderately associated with cancer risk (OR = 1.12, 95% CI = 1.01–1.24) in an additive genetic model (Fig. 2). In the subgroup analysis by cancer type, there was a significant association with risk of colorectal cancer (OR = 1.12, 95% CI = 1.04–1.21). In contrast, the MC4R rs17782313 SNP was not associated with endometrial cancer (OR = 1.12, 95% CI = 0.87–1.45) or breast cancer (OR = 1.27, 95% CI = 0.77–2.11) (Table 2).

After adjusting for BMI, the MC4R rs17782313 SNP risk allele was not associated with cancer risk (OR = 1.08, 95% CI = 0.94–1.23; Fig. 3). In the subgroup analysis by cancer type, the MC4R rs17782313 SNP was moderately associated with the risk of colorectal cancer (OR = 1.11, 95% CI = 1.03–1.20; Table 2). While the risk factor of the other 2 cancer type (endometrial cancer and breast cancer) were both not associated with the rs17782313 with and without adjustment for BMI.

### 3.3. Publication bias

There was no publication bias for the MC4R rs17782313 SNP using Begg test (\(P = .432\)) or Egger test (\(P = .275\)) before adjusting for BMI, as well as after adjusting for BMI (\(P = .308 \text{ and .310}, \text{respectively}).

### 4. Discussion

To our knowledge, this is the first meta-analysis that investigated the association between a SNP near the MC4R gene and risk of cancer. The present meta-analysis revealed that the MC4R rs17782313 SNP is moderately associated with risk of cancer, without adjusting for BMI. However, this association disappeared after adjusting for BMI. It appears that the association between the MC4R gene SNP and cancer risk may be mediated through adiposity.
Several previous GWAS have identified a large number of SNPs associated with obesity. The FTO gene is one of the first loci identified for obesity risk by GWAS. A most recent meta-analysis conducted by Kang et al revealed that the FTO gene rs9939609 SNP was not significantly associated with risk of cancer, regardless of the adjustment for BMI. However, in the subgroup analysis, this variant moderately increased the risk of endometrial cancer and pancreatic cancer, which was mediated by adiposity. Similarly, the authors also found a significant association between the MC4R gene rs17782313 SNP and risk of cancer, which mediated through BMI. Notably, a recent large-scale study suggested that MC4R gene SNPs are not associated with risk of cancer.

### Table 1

Characteristics of studies included in the meta-analysis.

| Cancer type          | Country       | Race/ethnicity | Sample size (cases/controls) | Men, % | Age, y | BMI, kg/m² (cases/controls) | OR (95% CI) | Adjusted covariates |
|----------------------|---------------|----------------|-------------------------------|--------|-------|-----------------------------|--------------|---------------------|
| Tenesa et al, 2009   | Colorectal cancer | UK             | European 799 vs 782           | NA     | <55   | 26.9 ± 5.0/27.1 ± 5.2      | 1.11 (0.96–1.28) | Gender and age |
| Delahanty et al, 2011| Endometrial cancer | China         | East Asian 832 vs 2049        | All were women | 30–69 | Overweight rate (57.7%/33.3%) | 1.29 (1.11–1.50) | Age, income, and education |
| Lurie et al, 2011    | Endometrial cancer | Australia, USA, Poland, Canada | European 2619 vs 3900         | All were women | 61.5 ± 8.9/59.7 ± 9.7 | NA | 0.99 (0.91–1.07) | Age |
| Kusinska et al, 2012 | Breast cancer | Poland          | European 134 vs 367           | All were women | 57.45 | NA | 0.94 (0.86–1.02) | Age and BMI |
| Lim et al, 2012      | Colorectal cancer | USA            | Mixed 2033 vs 9640            | 55%/55% | 70.0 ± 8.6/68.0 ± 8.6 | 27.2 ± 4.9/26.8 ± 4.8 | 1.12 (1.02–1.22) | Age, gender, and ethnicity |
| da Cunha et al, 2013 | Breast cancer | Brazil          | European (80%)                | All were women | 24–86/25–80 | Overweight rate (63%/57%) | 1.70 (1.02–2.98) | Age and BMI |

NA = not available.
colorectal cancer, regardless of adjusting for BMI.\[14\] However, that study did not focus on the rs17782313 SNP, which is the interest of the present study.

The mechanism underlying the association between the \textit{MC4R} SNP and cancer risk remains unclear. Similar to the \textit{FTO} gene, the \textit{MC4R} gene is also highly expressed in the central nervous system, which regulates the energy metabolism.\[19\] It was reported that MC4R may regulate food choice and intake, and energy expenditure through a distinct pathway.\[20,21\] However, further studies are needed to clarify the potential biological pathways through which these \textit{MC4R} SNPs increase the risk of obesity and cancer.

It is important to focus on an organ system, which might encompass two or more different cancer types (eg, genitourinary cancer). However, merely 6 studies met the inclusion criteria. Thus, an analysis that focused on an organ system could not be performed. In addition, it is also important to assess the association between SNPs and different endocrine-driven cancers. However, due to the unavailability of data, subgroup analysis was performed by cancer type (colorectal cancer, endometrial cancer and breast cancer).

The present study had 2 strengths. First, the OR was extracted with 95% CI, with the adjustment of covariates from individual studies, to calculate the summary estimate, which represents an accurate estimate. Second, a total 6517 cancer cases and 16,886 healthy controls were included in the present meta-analysis, which greatly improved the statistical power. However, 2 limitations should be considered. First, although the total sample

### Table 2

Meta-analysis of the association between \textit{MC4R} rs17782313 and cancer risk by cancer type.

|                        | No of studies (cases/controls) | OR (95% CI) | P z-test | I² (%) | P\(_{\text{heterogeneity}}\) | Statistical model |
|------------------------|--------------------------------|-------------|----------|--------|----------------------------|------------------|
| **Without adjustment for BMI** |                                |             |          |        |                            |                  |
| Total                  | 6 (6517/16886)                 | 1.12 (1.01-1.24) | .029    | 62.7   | .020                       | Random           |
| Colorectal cancer      | 2 (2832/10422)                 | 1.12 (1.04-1.21) | .004    | 0.0    | .917                       | Fixed            |
| Endometrial cancer     | 2 (3451/5949)                  | 1.12 (0.87-1.45) | .387    | 89.1   | .002                       | Random           |
| Breast cancer          | 2 (234/519)                    | 1.27 (0.77-2.11) | .356    | 57.1   | .127                       | Fixed            |
| **With adjustment for BMI** |                                |             |          |        |                            |                  |
| Total                  | 4 (5551/14470)                 | 1.08 (0.94-1.23) | .263    | 75.2   | .007                       | Random           |
| Colorectal cancer      | 2 (2832/10422)                 | 1.11 (1.03-1.20) | .008    | 0      | 1.000                      | Fixed            |
| Endometrial cancer     | 1 (2619/3900)                  | 0.94 (0.86-1.02) | .155    | —      | —                          | —                |
| Breast cancer          | 1 (100/148)                    | 1.66 (1.05-2.65) | .032    | —      | —                          | —                |

Figure 3. The meta-analysis of the association between \textit{MC4R} rs17782313 and cancer risk with the adjustment for body mass index.
size was sufficiently large, merely 6 studies were included. In addition, the subgroup analysis by cancer type should be interpreted with caution due to the limited studies available for each cancer type. Second, there was a significant between-study heterogeneity in the meta-analysis, even although a random effects model was used to overcome this limitation. In addition, the further meta-regression analysis did not reveal any potential confounders that may explain the between-study heterogeneity.

In summary, there might be an association between the MC4R rs17782313 SNP and risk of cancer, which might be mediated by adiposity. Further studies are necessary to identify the causal variant near the MC4R gene, as well as the underlying mechanism between the MC4R gene SNP and risk of cancer.

Author contributions

Conceptualization: Zeng Tian, Hongjun Xie.
Data curation: Xiaojiao Wang.
Formal analysis: Xiaojiao Wang.
Investigation: Zeng Tian.
Methodology: Jing Zhao, Yu Kang.
Supervision: Yu Kang.
Validation: Jing Zhao.
Visualization: Jing Zhao.
Writing – original draft: Zeng Tian, Jing Zhao, Hongjun Xie.
Writing – review & editing: Hongjun Xie.

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