Is FTO gene variant related to cancer risk independently of adiposity? An updated meta-analysis of 129,467 cases and 290,633 controls

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ABSTRACT

Previous studies have examined the association between the fat mass and obesity-associated (FTO) gene variant and risk of cancer in diverse populations. However, the results have been inconsistent. PubMed and Embase databases were searched for the eligible publications in English language by July, 2016. The associations of FTO variants with cancer risk were estimated by calculating the pooled odds ratios and 95% confidence intervals by meta-analyses. A total of 27 publications (129,467 cancer cases and 290,633 normal controls) were included in our meta-analysis. Overall, FTO rs9939609 variant (or its proxy) was not associated with cancer risk without adjustment for body mass index, as well as additional adjustment for body mass index. However, FTO rs9939609 variant was associated with some types of cancer in the subgroup analysis. In addition, overall, there was no significant association between FTO rs1477196 variant and cancer risk regardless of adjustment for body mass index. However, FTO rs11075995 variant risk allele was associated with breast cancer risk without adjustment for body mass index, but the association disappeared with further adjustment for body mass index. This study overall does not support that the FTO variant is associated with cancer risk independently of the adiposity.

INTRODUCTION

In 2007, the fat mass and obesity associated (FTO) gene was reported as the first obesity related gene by the genome-wide association studies (GWAS) in Caucasian population [1, 2]. Subsequently, the following studies confirmed the positive associations between single nucleotide polymorphisms (SNPs) in/near FTO gene and obesity risk in diverse populations [3–5]. FTO gene was found to affect the function of the central nervous system, as well as adipose tissue at a peripheral level. As obesity is a well established risk factor for most types of cancer, it is interesting and important to investigate whether FTO SNPs are associated with risk of cancer. Up to now, a total of 27 publications have examined the associations between FTO SNPs and risk of cancer [6–32]. However, the results have been inconsistent. Three meta-analyses have summarized the associations between FTO SNPs and risk of cancer [33–35]; however, there are several limitations for them. First, they did not address whether the associations were mediated through body mass index (BMI)/obesity. Second, many eligible studies were omitted. Third, two of three from the same study team examined the association between each of two SNPs (rs8050136[34] and rs9939609[35]) in/near FTO gene and cancer risk. It is illogical to do the separate analyses for these two SNPs as they are in strong linkage disequilibrium (LD, r²>0.90) in both European and Asian populations.

Therefore, we aimed to perform an updated meta-analysis to investigate the associations between FTO rs9939609 SNP (or any proxy SNP, r²>0.90) and other SNPs which are not in tight LD with rs9939609 SNP (such as rs1477196 and rs11075995) and cancer risk. In addition, we also aimed to examine whether the associations are independent of adiposity.
RESULTS

Characteristics of the studies

A flow chart describing the process of inclusion/exclusion of studies is presented in Figure 1. The literature search identified a total of 238 potentially relevant articles. At last, a total of 27 publications (129,467 cancer cases and 290,633 normal controls) were included in our meta-analysis. There were 24 publications (113,780 cases and 210,593 controls) for FTO rs9939609 SNP, 5 publications (1594 cases and 2034 controls) for FTO rs1477196 SNP, and 3 publications (14144 cases and 79973 controls) for rs11075995 variant. All three SNPs in the each of included studies were in Hardy-Weinberg Equivalent. The characteristics of the included studies are listed in Table 1.

Meta-analysis results

Overall, FTO rs9939609 SNP was not associated with cancer risk without adjustment for BMI (OR=1.01, 95%CI=0.97-1.05). In the subgroup analysis by race/ethnicity, before adjustment for BMI, there was no any significant associations in European population, East Asian population, Middle East population and mixed population (all P>0.05) (Figure 2). After adjustment for BMI, FTO rs9939609 SNP risk allele was associated with cancer risk in East Asian population (OR=1.29, 95%CI=1.06-1.57) and African population (OR=1.21, 95%CI=1.06-1.38), but not in European population, Middle East population and Mixed population (all P>0.05) (Figure 3). In the subgroup analysis by cancer type, FTO rs9939609 SNP risk allele marginally increased risk of endometrial cancer (OR=1.07, 95%CI=1.00-1.14) and pancreatic cancer (OR=1.12, 95%CI=1.04-1.21), while it marginally decreased risk of breast cancer (OR=0.94, 95%CI=0.92-0.96) (Table 2 and Supplementary Figure 1). Overall, there was no significant association between FTO rs9939609 SNP and cancer risk with adjustment for BMI (OR=1.01, 95%CI=0.93-1.10). FTO rs9939609 SNP risk allele marginally decreased risk of prostate cancer (OR=0.93, 95%CI=0.88-0.99), while it marginally increased risk of breast cancer (OR=1.12, 95%CI=0.99-1.26) (Table 2 and Supplementary Figure 2).

There was no significant association between FTO rs1477196 SNP and cancer risk without (OR=1.07, 95%CI=0.97-1.20) or with (OR=1.08, 95%CI=0.97-1.21) adjustment for BMI. However, we found a significant association between FTO rs1477196 SNP and risk of thyroid cancer without (OR=1.31, 95%CI=1.07-1.61) or with (OR=1.32, 95%CI=1.08-1.62) adjustment for BMI (Table 2 and Supplementary Figures 3-4).

FTO rs11075995 SNP risk allele was associated with breast cancer risk without adjustment for BMI (OR=1.08,
Table 1: The detailed characteristics of the included studies in the meta-analysis

<table>
<thead>
<tr>
<th>Study *</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Type of cancer</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR</th>
<th>95% CI</th>
<th>SNP</th>
<th>Adjustment for BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brennan, 2009 [6]</td>
<td>Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia</td>
<td>European</td>
<td>Lung cancer</td>
<td>2250</td>
<td>3052</td>
<td>0.92</td>
<td>0.84</td>
<td>rs9939609</td>
<td>No</td>
</tr>
<tr>
<td>Brennan, 2009 [6]</td>
<td>Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia</td>
<td>European</td>
<td>Kidney cancer</td>
<td>954</td>
<td>3052</td>
<td>1.06</td>
<td>0.95</td>
<td>rs9939609</td>
<td>No</td>
</tr>
<tr>
<td>Brennan, 2009 [6]</td>
<td>Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia</td>
<td>European</td>
<td>Upper aerodigestive cancer</td>
<td>811</td>
<td>3052</td>
<td>0.98</td>
<td>0.87</td>
<td>rs9939609</td>
<td>No</td>
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<tr>
<td>Gaudet, 2010 [7]</td>
<td>USA and Australia</td>
<td>Mixed</td>
<td>Endometrial cancer</td>
<td>417</td>
<td>406</td>
<td>1.05</td>
<td>0.86</td>
<td>rs8050136</td>
<td>No</td>
</tr>
<tr>
<td>Lewis, 2010 [8]</td>
<td>UK</td>
<td>European</td>
<td>Prostate cancer</td>
<td>1550</td>
<td>1815</td>
<td>0.94</td>
<td>0.85</td>
<td>rs9939609</td>
<td>Yes</td>
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<tr>
<td>Meyer, 2010 [9]</td>
<td>USA</td>
<td>Mixed</td>
<td>Prostate cancer</td>
<td>379</td>
<td>5874</td>
<td>1.04</td>
<td>0.91</td>
<td>rs8050136</td>
<td>No</td>
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<td>Delahanty, 2011 [10]</td>
<td>China</td>
<td>East Asian</td>
<td>Endometrial cancer</td>
<td>832</td>
<td>2049</td>
<td>1.07</td>
<td>0.89</td>
<td>rs9939609</td>
<td>No</td>
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<tr>
<td>Kaklamani, 2011 [11]</td>
<td>USA</td>
<td>Mixed</td>
<td>Breast cancer</td>
<td>302</td>
<td>349</td>
<td>0.992</td>
<td>0.78</td>
<td>rs9939609</td>
<td>No</td>
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<td>Lurie, 2011 [12]</td>
<td>Australia, USA, Poland, and Canada</td>
<td>European</td>
<td>Endometrial cancer</td>
<td>3561</td>
<td>5167</td>
<td>1.07</td>
<td>0.99</td>
<td>rs9939609</td>
<td>No</td>
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<td>Pierce, 2011 [13]</td>
<td>Finland, USA, China, France, Germany, Greece, Italy, The Netherlands, Spain, and the UK</td>
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<td>Pancreatic cancer</td>
<td>1763</td>
<td>1802</td>
<td>1.12</td>
<td>1.02</td>
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<td>No</td>
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<td>Tang, 2011 [14]</td>
<td>USA</td>
<td>Mixed</td>
<td>Pancreatic cancer</td>
<td>1053</td>
<td>1130</td>
<td>1.08</td>
<td>0.96</td>
<td>rs9939609</td>
<td>No</td>
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<tr>
<td>Brooks, 2012 [15]</td>
<td>USA and Denmark</td>
<td>European</td>
<td>Breast cancer</td>
<td>643</td>
<td>1271</td>
<td>1.1</td>
<td>0.9</td>
<td>rs9939609</td>
<td>No</td>
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<tr>
<td>Hubacek, 2012 [16]</td>
<td>Czech Republic, Hungary, Poland, Romania, Russia, and Slovakia</td>
<td>European</td>
<td>Colorectal cancer</td>
<td>1005</td>
<td>6827</td>
<td>1.02</td>
<td>0.93</td>
<td>rs17817449</td>
<td>No</td>
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<tr>
<td>Kitahara, 2012 [17]</td>
<td>USA</td>
<td>European</td>
<td>Thyroid cancer</td>
<td>341</td>
<td>444</td>
<td>0.77</td>
<td>0.62</td>
<td>rs9939609</td>
<td>No</td>
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</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Type of cancer</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR</th>
<th>95% CI</th>
<th>SNP</th>
<th>Adjustment for BMI</th>
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</thead>
<tbody>
<tr>
<td>Kusinska, 2012 [18]</td>
<td>Poland</td>
<td>European</td>
<td>Breast cancer</td>
<td>134</td>
<td>357</td>
<td>1.32</td>
<td>1.05</td>
<td>1.61</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Lim, 2012 [19]</td>
<td>USA</td>
<td>Mixed</td>
<td>Colorectal cancer</td>
<td>2033</td>
<td>9640</td>
<td>1.05</td>
<td>0.93</td>
<td>1.11</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Machiela, 2012 [20]</td>
<td>USA and several European countries</td>
<td>European</td>
<td>Prostate cancer</td>
<td>2782</td>
<td>4458</td>
<td>0.93</td>
<td>0.86</td>
<td>1.00</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Tarabra, 2012 [21]</td>
<td>Italy</td>
<td>European</td>
<td>Colorectal cancer</td>
<td>341</td>
<td>311</td>
<td>1.01</td>
<td>0.81</td>
<td>1.25</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Akilzhanova, 2013 [22]</td>
<td>Kazakhstan</td>
<td>European</td>
<td>Breast cancer</td>
<td>315</td>
<td>604</td>
<td>0.96</td>
<td>0.78</td>
<td>1.17</td>
<td>rs1477196</td>
</tr>
<tr>
<td>da Cunha, 2013 [23]</td>
<td>Brazil</td>
<td>European</td>
<td>Breast cancer</td>
<td>100</td>
<td>148</td>
<td>0.86</td>
<td>0.60</td>
<td>1.25</td>
<td>rs9939609</td>
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<td>Garcia-Closas, 2013 [24]</td>
<td>USA and many European countries</td>
<td>European</td>
<td>Breast cancer</td>
<td>10706</td>
<td>76647</td>
<td>1.11</td>
<td>1.07</td>
<td>1.15</td>
<td>rs11075995</td>
</tr>
<tr>
<td>Iles, 2013 [25]</td>
<td>European countries</td>
<td>European</td>
<td>Melanoma</td>
<td>13060</td>
<td>60726</td>
<td>1.03</td>
<td>0.97</td>
<td>1.10</td>
<td>rs8050136</td>
</tr>
<tr>
<td>Lin, 2013 [26]</td>
<td>Japan</td>
<td>East Asian</td>
<td>Pancreatic cancer</td>
<td>360</td>
<td>400</td>
<td>1.33</td>
<td>1.04</td>
<td>1.72</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Long, 2013 [27]</td>
<td>USA</td>
<td>African</td>
<td>Breast cancer</td>
<td>1113</td>
<td>930</td>
<td>1.21</td>
<td>1.06</td>
<td>1.37</td>
<td>rs17817449</td>
</tr>
<tr>
<td>Zheng, 2013 [28]</td>
<td>China, Korea, Japan and Thailand</td>
<td>East Asian</td>
<td>Breast cancer</td>
<td>16797</td>
<td>18983</td>
<td>0.92</td>
<td>0.88</td>
<td>0.97</td>
<td>rs17817449</td>
</tr>
<tr>
<td>Zhang, 2014 [29]</td>
<td>China</td>
<td>East Asian</td>
<td>Breast cancer</td>
<td>2901</td>
<td>2789</td>
<td>1.06</td>
<td>0.98</td>
<td>1.14</td>
<td>rs11075995</td>
</tr>
<tr>
<td>Mojaver, 2015 [30]</td>
<td>Iran</td>
<td>Middle East</td>
<td>Breast cancer</td>
<td>99</td>
<td>100</td>
<td>0.85</td>
<td>0.51</td>
<td>1.41</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Zeng, 2015 [31]</td>
<td>China</td>
<td>East Asian</td>
<td>Breast cancer</td>
<td>537</td>
<td>537</td>
<td>1.19</td>
<td>0.90</td>
<td>1.57</td>
<td>rs9939609</td>
</tr>
<tr>
<td>Zhao, 2016[32]</td>
<td>Several European countries</td>
<td>European</td>
<td>Breast cancer</td>
<td>62328</td>
<td>83817</td>
<td>0.94</td>
<td>0.92</td>
<td>0.95</td>
<td>rs9939609</td>
</tr>
</tbody>
</table>

* All included studies were case-control designed.
95%CI=1.01-1.15) (Table 2 and Supplementary Figure 5). However, the significant association disappeared after adjustment for BMI (OR=1.08, 95%CI=0.89-1.31) (Table 2 and Supplementary Figure 6).

**Publication bias**

There was no publication bias for *FTO* rs9939609, rs1477196 or rs11075995 SNP using Begg’s test or Egger’s test (all \(P>0.05\)).

**DISCUSSION**

Our updated meta-analysis shows that *FTO* rs9939609 SNP was associated with some types of cancer, such as endometrial cancer, pancreatic cancer and breast cancer without adjustment for BMI, while it was still associated with breast cancer and prostate cancer with adjustment for BMI. In addition, *FTO* rs1477196 SNP was associated with thyroid cancer independently of BMI and *FTO* rs11075995 SNP was associated with breast cancer dependently on BMI.

![Figure 2: Forest plot of the effect of *FTO* rs9939609 on risk of cancer by race/ethnicity without adjustment for body mass index.](image-url)
Several meta-analyses have addressed the association between FTO SNP and risk of diabetes, hypertension, cardiovascular disease, polycystic ovary syndrome and mortality. Most of these meta-analyses supported FTO SNP was associated with health outcomes independently of adiposity. A meta-analysis of data from 169,551 Caucasian adults showed that the hazards ratio (HR) for the A minor allele of the FTO rs9939609 SNP was 1.02 (1.00–1.04, P=0.097), but the association disappeared after adjustment for BMI (HR=1.00; 0.98–1.03, P=0.662). These results suggested that FTO SNP risk allele increases risk of mortality directly through adiposity pathway.

It seemed that FTO rs9939609 SNP played different roles in the development of different cancer, as well as in different populations. Previous studies demonstrated that BMI was associated with risk of common cancer, but its association with some cancer types differed between sexes and different ethnic populations. As FTO SNP rs9939609 was strongly associated with BMI, it is not surprising that this variant was associated with some types of cancer but not with other types of cancer.

The FTO protein is highly expressed in hypothalamus, as well as in many other tissues: mesenteric fat, adipose, pancreatic, and liver. It regulates the global metabolic rate, energy expenditure, energy homeostasis, body size and body fat accumulation. FTO SNP rs9805136 was reported to preferentially bind to cut-like homebox (CUTL1) in human fibroblast DNA and silencing this transcriptional factor CUTL1 could lead to decreased FTO expression in fibroblasts. In addition, FTO SNP was strongly associated with expression of a tumor suppressor/cell cycle-
repressing gene, namely retinoblastoma-like 2 [44]. Further studies are necessary to clarify the underlying mechanism between FTO SNP and cancer risk.

Our study has several strengths. First, our study included 27 publications consisting of ~130,000 cases and ~300,000 controls, which had the larger statistical power than three previous meta-analyses [33–35]. Second, we presented results without and with adjustment for BMI, but the previous three meta-analyses didn’t. Third, besides rs9939609 and its proxy SNP (rs8050136...
and rs17817449), we also investigated two other SNPs (rs1477196 or rs11075995), which are not in high LD with rs9939609. However, several limitations should be noted. First, the effects of gene-gene/gene-environment interactions were not addressed in this meta-analysis as the included individual studies did not provide us with these data. Second, although the total sample size was large enough, it was still limited for some types of cancer. Thus, the subgroup results with limited statistical power should be interpreted with caution. Third, there was significant heterogeneity between studies for three SNPs and the results should be interpreted cautiously.

In conclusion, our updated meta-analysis supported that FTO SNP was associated with some types of cancer, which was mediated by BMI or independent of BMI. Further studies should focus on gene-gene/gene-environment interaction in the development of cancer. Epigenetics and metabonomics should be paid more attention in order to solve how BMI modify the association between FTO SNP and cancer risk.

**MATERIALS AND METHODS**

**Literature and search strategy**

We searched PubMed and Embase databases for the potentially eligible studies. The following key words were used to search the eligible publications: (fat-mass and obesity-associated gene OR FTO) and (polymorphism OR variant OR variation OR genotype) and (cancer OR tumor OR carcinoma). We restricted publication language to English. The reference lists of retrieved articles were also hand-searched. The literature search was updated by July 14, 2016.

**Inclusion criteria and data extraction**

The included studies met all the following inclusion criteria: (1) investigation of the association of FTO rs9939609 SNP (or any proxy SNP (rs8050136, rs17817449), $r^2>0.90$) or other SNPs which are not in tight LD with rs9939609 (such as rs1477196 and rs11075995) with cancer risk; (2) use of a case–control or cohort design; and (3) provision of an odds ratio (OR) with 95% confidence interval (CI) with or without adjustment for body mass index (BMI). The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) race/ethnicity of the study population; (5) number of cases and controls; (6) type of cancer; (7) studied SNP; and (8) whether adjusted for BMI in the logistical regression model. Two authors independently reviewed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision after discussion with the third author.

**Statistical analysis**

The associations of FTO SNPs with cancer risk were estimated by calculating the pooled ORs and 95% CIs under an additive genetic model. The significance of the OR was determined by the Z test ($p<0.05$ was considered statistically significant). Cochrane’s Q test was performed to test the between-study heterogeneity [45, 46]. $F$ represents the range for degree of heterogeneity. A random-effects (DerSimonian–Laird [45]) or fixed-effects (Mantel–Haenszel [46]) model was used to calculate the pooled OR in the presence ($p<0.10$ or $F<50\%$) or absence ($p>0.10$ and $F<50\%$) of heterogeneity, respectively. Publication bias was assessed by Begg’s test and Egger’s test [47] ($p<0.05$ was considered statistically significant). Data were analyzed using STATA version 11.0 (StataCorp LP, College Station, TX, USA).

**Author contributions**

Y.L. conceived, designed and supervised the study. Y.K. wrote the manuscript. Y.K. and F.L. searched the databases, extracted and analyzed the data. All authors reviewed and approved the final manuscript.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**REFERENCES**

The authors declare no conflicts of interest.


