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The Association of Adiponectin and *AdipoR1* Polymorphism rs1342387 in Some Obesity-related Cancers in Kurdistan Iraq

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Adiponectin (APN) is a novel hormone produced mainly by white adipose tissue that contribute to various physiological functions. APN has been related to cancer development specially the ones related to obesity such as breast cancer (BC) and colorectal cancer (CRC). Therefore, it also has been related body mass index (BMI). This study aims to investigate the role of APN and *AdipoR1* polymorphism rs1342387 in some obesity-related cancer patients living in Erbil province (Kurdistan-Iraq).
Method: The study includes 82 subjects (66 cancer patients, 16 healthy controls) from 4 medical facilities in Erbil, all participants were subjected to a questionnaire and signed a consent form before taking the samples. The serum level of APN was estimated by ELISA and the *AdipoR1* polymorphism (rs1342387) was detected by RFLP-PCR.
Results: The results showed that the prevalence of BC cases were more than CRC cases. Furthermore, females were the dominant sex in BC. Moreover, the level of APN was significantly decreased in obesity-related cancer groups (BC, CRC) in compare to HC. Regarding APN

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correlation with BMI the results showed a weak non-significant negative correlation. The attempt to investigate the genotype of Kurdish people showed the frequency of GG genotype among Kurdish people but the recessive AA genotype showed more effects on decreasing the level of APN despite the non-significant results.

Conclusion: This study is the first to investigate *AdipoR1* polymorphism and its correlation to obesity-related cancers in Kurdistan-Iraq and although GG was the more frequent genotype, AA was more effective on APN levels in obesity-related cancers.

Keywords: APN; AdipoR1; polymorphism; cancer; obesity.

1. INTRODUCTION

Cancer is the second leading death worldwide only preceded by heart diseases causing 9.6 million deaths in 2018 [1, 2]. In Kurdistan region, cancer cases were increased in comparison to the past years [3]. Several risk factors for cancer were identified such as smoking [4]. Chemical substances, heavy metals, radiation and other mutagens [5, 6]. In addition to infections [7].

Breast cancer (BC) is the most common cancer in women worldwide and the leading cause of death for them [8]. BC incidence rates are increased worldwide, especially in developing nations [9]. It is also the most common female cancer in Kurdistan Iraq with an incidence rate of 17.1 per 100000 per year at all ages [10, 11]. Different etiological and risk factors affect BC such as according to the geographical locations [12] age, family history, increased reproductive years, obesity, low physical activities and several dietary factors [13-15]. Colorectal cancer (CRC) is ranking fourth among the commonest cancers worldwide [16]. However, it comes third in Kurdistan-Iraq [17]. Similar to BC, several recognized risk factors for CRC including increasing age, dietary habits, obesity, decreased physical activity and smoking [18]. The incidence of CRC in Iraq is raising from 2.75% to 3.26% in the last 2 decades compared to 6-13% in the developed countries [19].

Obesity is a complex, multifactorial, prevalent highly preventable disease affecting one 3rd of the world together with overweight [20-22]. By 2030, it is expected to affect 38% of the adults worldwide [23]. It remarkably increases the risk of chronic disease morbidity specifically disability, depression, type 2 diabetes mellitus, cardiovascular disease, different cancers [24]. Although some studies indicate that other indicators of obesity may be better predictors of obesity-related complications, BMI is still the most widely used indicator [25].

The International Agency for Research on Cancer (IARC] study in 2002 indicated that weight gain avoidance may have cancer preventive effect on decreasing the risk of 5 cancer types including colon, esophagus, kidney and breast while the evidence for lowering cancer risk by the absence of body fatness was clarified for 8 cancers including gastric cardia, liver, gallbladder, pancreas, ovary, thyroid, multiple myeloma and meningioma [26]. Circulating estradiol levels is directly affected by obesity in postmenopausal women [27], and BC risk is directly related to estradiol levels [28]. Losing 10 kg after menopause may decrease BC risk by 50% which is similar to the effect of smoking cessation on lung cancer [29]. In CRC it seems that insulin pathways may mediate the effect of BMI [30].

APN is an adipocytokine that is mainly produced by white adipose tissue and secreted into the plasma forming the most available adipocytokine in plasma [31]. A small percentage of APN is secreted by several other tissues including brown adipose tissue, colon, skeletal muscle, salivary glands, fetal tissue, liver and placenta [32, 33]. Various factors including hormones, inflammatory processes, genetic polymorphisms, nutritional status and drugs affect APN level [34]. APN acts through three receptors namely AdipoR1, adipoR2 and T-cadherin [35]. From information above it has been hypothesized that because these conditions are known risk factors for breast and colon cancers APN might be behind this association [36, 37]. APN which its receptors are expressed in many cancers, may have different effects on cancer cells inhibiting tumor proliferation and angiogenesis in most conditions while supporting cancer cell survival during glucose deprivation [38, 39]. Moreover, AdipoR1 polymorphism including rs1342387 was reported to have an association with higher risk for cancer [40].

Our aim is to investigate APN level in obesity-related cancers (like BC and CRC) in Kurdistan

region and its correlation to BMI, in addition, investigate the association of *AdipoR1* polymorphism rs1342387 with high risk for those cancers compared to healthy controls.

2. METHODS

The study was conducted using a cross-sectional design in the health facilities of Erbil city the capital of Iraqi Kurdistan Region. Venous blood samples from cancer patients (n=66) (51 breast cancers (BC), 15 colorectal cancers (CRC)) were collected from four medical facilities (Nanakaly hospital for blood disease and cancer, Rizgary hospital, Shaqlawa teaching hospital, and Malaika Rahma Private Clinic) in addition, 16 venous blood samples were collected from healthy individuals (apparently healthy and cancer free individuals). All samples were stored at -20^0 C until further analyses. Information regarding age, sex, height, weight were collected from the questionnaire. The BMI was calculated for each sample according to the BMI formula as follow:

$$Body\ Mass\ Index = \frac{Weight}{Height\ (m)^2}$$

Serum samples were separated from all samples and the serum level of APN was estimated by Enzyme Linked ImmunoSorbent Assay (ELISA) using Human APN ELISA kit (Shanghai Korain Biotech Company) with the use of Biotek ELX50 Microplate Strip Washer and BioTek ELX800 Microplate reader. The ELISA was performed according to manufacturer protocol.

DNA was extracted from the blood samples of the study subjects using the DNA extraction kit (ReliaPrep™ Blood gDNA Miniprep System, USA) which was performed according to the manufacturer protocol.

The amplification of rs1342387 polymorphisms of *AdipoR1* were carried out using a pair of primers. *Adipor1-F*: 5'- CACCTGGTAGTGGGATTGG-3', *Adipor1-R*: 5'- GAGAAGCTGAGGCAGAGCA-3'. In a 50 µl reaction, The thermal cycler conditions were 95 ˚C for 5 min., 35 cycles of 95 ˚C for 30 sec., 56 ˚C for 45 sec. and 72 ˚C for 30 sec. followed by a final extension step of 72 ˚C for 10 min. the PCR product were then digested by *Bcc1* CutSmart™ Buffer (Biolabs, England) according to the standard protocol of the manufacturer. The mixture was incubated for 1 hour at 37 ˚C. The RFLP-PCR result fragments were separated in 1% Agarose gel using standard procedures for agarose preparation and running the gel electrophoresis.

The data underwent statistical analysis using Mann-Whitney Confidence Interval. In addition, the odd ratios and the 95% confidences interval (CI) for the detected genotypes were calculated. The test is significant at $P<0.05$.

3. RESULTS

The mean age of all participants in this study was 50.41±1.31yrs. The mean ages of BC, CRC and HC were 48.82±7.14 with a range starts from 24 to 70 years, 55.8±2.95 with a range starts from 30 to 67 and 31.06±2.8 with a range of 18 to 52 years, respectively. In regard of the sex of study subjects, the majority of cancer patients, collectively, were females (56 patients representing about 85% of the patients and 10 healthy controls or about 62%). All BC patients were females (100%) while in CRC 66.6% of the patients were males. In HC the majority of participants were females as well as shown in Table 1.

From the BMI's formula, the values of BMI for each participant were calculated and categorized into 4 categories: **1.** Underweight (BMI<18.5) **2.** Normal weight (BMI=18.5-24.9) **3.** Overweight (BMI=25-29.9) **4**. Obese (BMI>30). The results showed that the majority of cancer patients have high value of BMI and falls within the overweight and obese categories. The distribution of the study subjects according to the BMI's categories is demonstrated in Table 2.

Table 1. The distribution of study subjects according to sex

Groups	Females (%)	Males (%)	Total (%)
BC	51 (100%)	0 (0%)	51 (100%)
CRC	5 (33.3%)	10 (66.6%)	15 (100%)
Total	**56 (84.8%)**	**10 (15.2%)**	**66 (100%)**
HC	10 (62.5%)	6 (37.5%)	16 (100%)
Total	**66 (80.5%)**	**16 (19.5%)**	**82 (100%)**

The results of the estimation of serum APN level showed a significant decrease APN levels obesity-related cancer patients in compare to HC (*P*=0.03). The results showed also a significant decrease in APN level in compared to HC (*P*=0.02). The mean of APN levels were 6.68 ± 2.64, 5.95±1.61 and 19.75±7.97 mg/l, for BC, CRC and HC respectively (Fig. 1).

Table 2. The distribution of study subjects according to BMI categories

Groups	BMI categories			
	Underweight (<18.5)	Normal weight (18.5-24.9)	Overweight (25-29.9)	Obese (>30)
BC	2	13	14	22
CRC	0	6	5	4
HC	1	10	1	4
Total	**3**	**29**	**20**	**30**

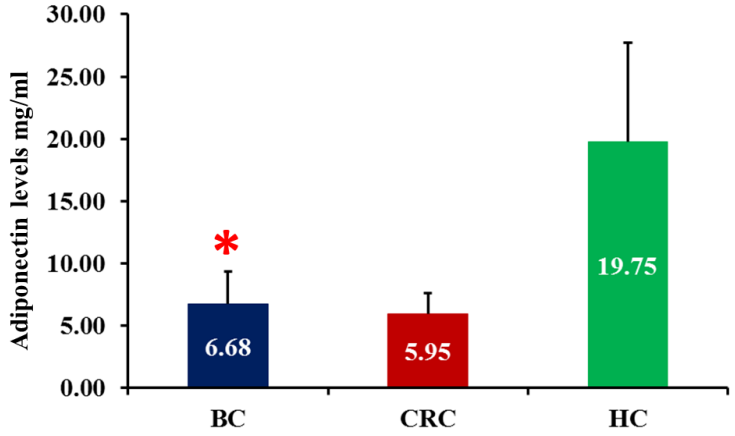

Fig. 1. APN level in obesity-related cancer. The serum level of APN was measured using ELISA. The level of APN was significantly decreased in BC and in CRC patients in comparison to HC (6.68 ± 2.64, 5.95±1.61 and 19.75±7.97 mg/l, respectively)

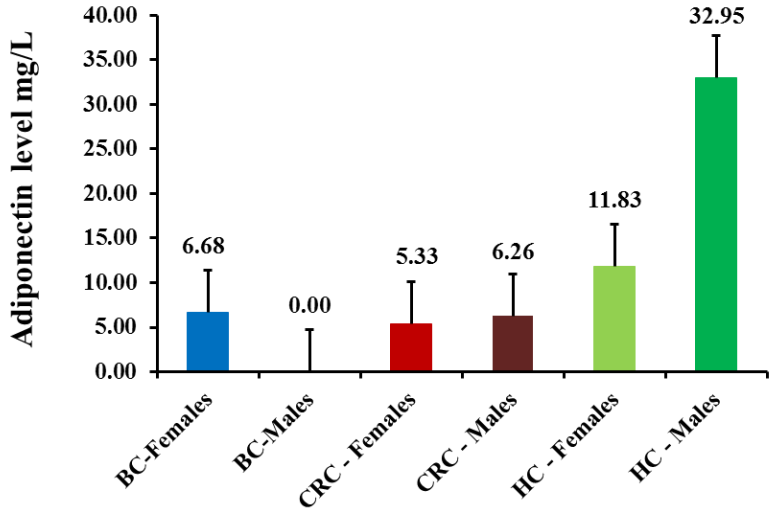

Fig. 2. APN levels in obesity-related cancer patients according to sex. The serum level of APN was measured using ELISA. For BC-males no males samples for BC were collected during the study

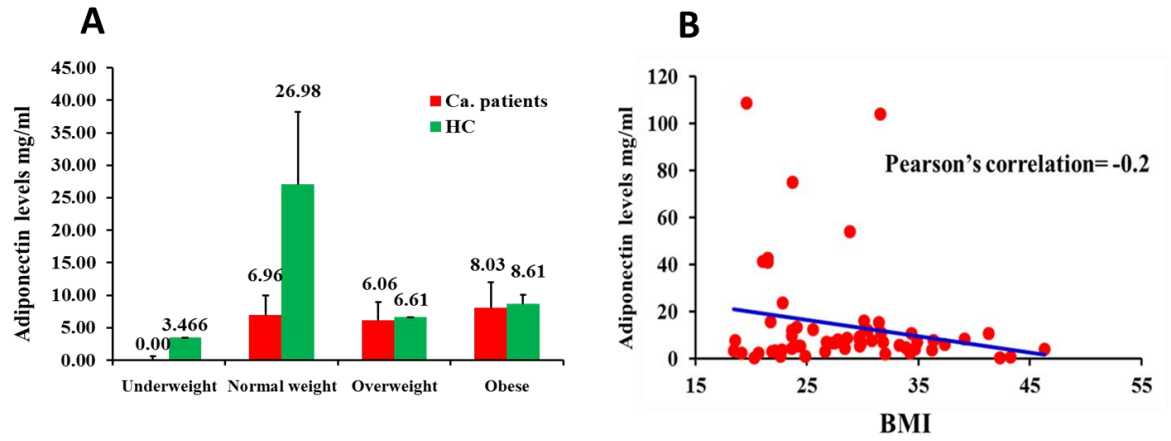

Fig. 3. APN correlation with BMI. (A). APN levels differences according to BMI in obesity-related cancer patients in compared to HC. (B). A Pearson's correlation between APN levels and BMI in obesity-related cancer patients in compared to HC. The Pearson's correlation value of – 0.2 represent a weak non-significant negative correlation between APN level and BMI The serum level of APN was measured using ELISA

Table 3. Genotypes frequency of *AdipoR1* rs1342387 polymorphism in study groups

Genotype	Ca. (%)	HC (%)	OR	95% CI	P value
Codominant model					
GG	12 (63.2%)	6 (42.9%)	1.00	-	-
AA	5 (26.3%)	7 (50%)	2.8	0.61-12.6	0.18
GA	2 (10.5%)	1 (7.1%)	1.0	0.07-13.36	1.00
Dominant model					
GG	12 (63.2%)	6 (42.9%)	1.00	-	-
GA/AA	7 (36.8%)	8 (57.1%)	2.28	0.55-9.36	0.25
Recessive model					
GG/GA	14 (73.7%)	7 (50%)	1.00	-	-
AA	5 (26.3%)	7 (50%)	2.8	0.65-12.1	0.16
Over-dominant model					
GG/AA	17 (89.5%)	13 (92.9%)	1.00	-	-
GA	2 (10.5%)	1 (7.1%)	0.56	0.05-8.02	0.73

There were no significant differences between females and males in APN levels in BC and CRC and HC groups (p>0.05). The mean levels were 6.68 ± 2.64, 0±0 (No males in BC), 5.33±0.74, 6.26±2.42, 11.83±4.00 and 32.95±20.11mg/l, respectively. However, there was a trend toward less APN level in females in obesity-related cancer patients (CRC) and HC compared to males (Fig. 2).

The results showed a trend toward decreased APN levels in obesity-related cancer patients and HC according to various BMI but with no statistical significance (*P*>0.05) (Fig. 3A). Moreover, the Pearson correlation showed a weak non-significant negative correlation between APN level and BMI (Pearson's correlation = -0.2) as shown in Fig. 3B.

In this study the genotype and allele frequencies of the *AdipoR1* polymorphisms (rs1342387) were detected in only a total of 33 participants (due to Corona virus pandemic and the curfew we could not order additional materials) was as follow:

BccI restriction enzyme was used to detect the rs1342387 polymorphism which contain certain restriction sites depended on G/A nucleotides, From the study groups 19 of cancer group (BC=10, CRC=9) and 14 of HC were genotyped and the results showed that RFLP-PCR products were observed as either two homozygous (GG and AA) or a heterozygous (AG). The resulting fragments were 474, 294 and 180 bp after digestion. GG genotype appeared as one band 474 bp, AA genotype appeared as two bands 294 and 180 bp, AG genotype appeared as three bands including 474, 294 and 180 bp.

Table 4. Alleles frequency of *Adipor1* polymorphism in study groups

Allele	Frequency (%)	HC (%)	OR	95% CI	P value
Cancer groups					
G allele	26 (68.4%)	13 (46.4%)	1.00	-	-
A allele	12 (31.6%)	15 (53.6%)	0.403	0.099-1.64	0.2
BC group					
G allele	14 (70%)	13 (46.4%)	1.00	-	-
A allele	6 (30%)	15 (53.6%)	2.7	0.8-9.03	0.1
CRC group					
G allele	12 (66.7%)	13 (46.4%)	1.00	-	-
A allele	6 (33.3%)	15 (53.6%)	2.3	0.67-7.89	0.1

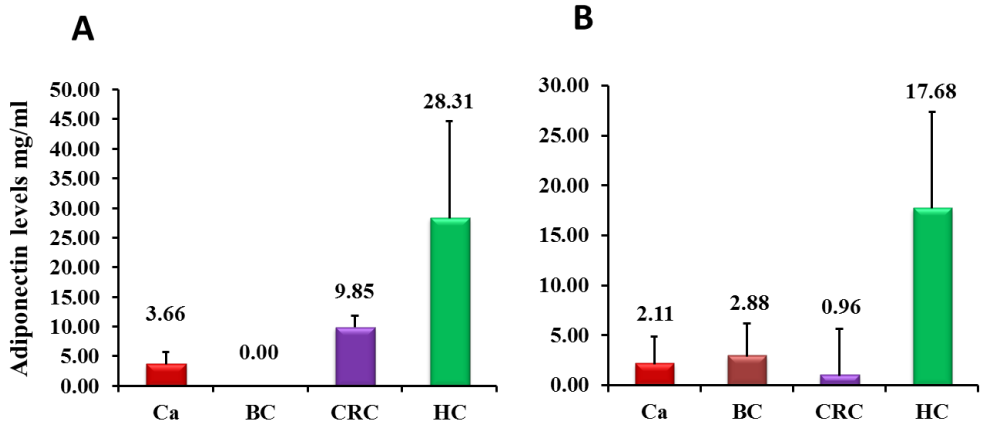

Fig. 4. APN levels according to *AdipoR1* polymorphism genotypes. (A). APN levels in obesity-relatedcancer groups according to the GG genotype of *AdipoR1* polymorphism. (B). APN levels in obesity-related cancer groups according to the AA genotype of *AdipoR1* polymorphism. The serum level of APN was measured using ELISA

No significant association of AdipoR1 gene polymorphism and the risk of developing BC or CRC was found in the present study under the probability of $P < 0.05$ but the results showed that GG genotype is more frequent in all groups. The odd ratios, 95% confidence interval and the p values using the 4 genetic models is shown in Table 3. The frequency of the G allele was high in obesity-related cancer group in both BC and CRC 68.4%, 70% and 66.7% respectively while its frequency in HC was 46.4%. The frequency of the A allele was less in cancer group in both BC and CRC 31.6%, 30% and 33.3% respectively while its frequency in HC was 53.6% . The odd ratios, 95% confidence interval and the p values were calculated as shown in Table 4.

The results the levels of APN were non significantly decreased in obesity-related cancer patients (P=0.22) in compare to HC group. Looking at the type of cancer, the results showed a significant decrease in APN in BC in compare to CRC and HC (P=0.014 and P=0.04, respectively). The mean levels were 3.86±2.05, 0.0, 9.85±1.97 and 28.31±16.38 mg/ml, for cancer group collectively (Ca), BC, CRC and HC, respectively as shown in Fig. 4A. The results showed that the levels of APN were non significantly decrease (P=0.484) in obesity-related cancer groups in compare to HC group. The mean levels were 2.11±2.78, 2.88±3.34, 0.96±4.69 and 17.68±9.73 mg/ml, respectively as shown in Fig. 4B.

4. DISCUSSION

The study is a small cross-sectional design with random selection of patients with with obesity-related cancers including breast and colon cancer in addition to healthy controls. To the authors knowledge this is the first study to investigate APN level and AdipoR1 polymorphism cancer patients in Iraq Kurdistan (Erbil). The present study dealt with two of the most common cancers BC and CRC and tried to have an insight look of APN role during these

cancers and its relation to the risks that may increase their prevalence in Kurdistan Iraq especially Erbil.

In general the cancer incidence increased in the past few years in this area and many studies had reported such increase [41]. Cancer incidence in Erbil is higher in compare with other cities within Kurdistan Iraq region i.e. Sulaymaniyah and Duhok and it has been reported that Breast cancer (BC) is the dominant type of cancer in females living in Erbil, while colon cancer less prevalence [42]. Despite the less prevalence of colorectal cancer (CRC) in compare with BC but it's still one of the most common type of cancers in other cities such as Sulaymaniyah [43]. With the increased cases of cancer it is important to raise awareness among people living in this region to adapt healthier life style and eat healthy to decrease such spread [44].

Obesity, is a condition in which an individual has a BMI more than 30, it is a chronic condition that has an increased prevalence around the world, it considered as a cause of important health issues in most countries [45]. Several studies specially the large epidemiological ones have estimated the association between obesity and mortality in general. For example, a meta-analysis of 230 cohort studies including > 30 million individuals reported that obesity and overweight were associated with an increased risk of all-cause mortality. BMI is an indicator of obesity which was related to cancer initiation in many studies and different types of cancers such as ovarian cancer, pancreatic cancer, colorectal cancer [46-48] and breast cancer [49].

In the present study, BC showed the strongest correlation between cancer risk and obesity this can be due to nature structure of the breast that is composed of about 80% of adipose tissue. This structure results in exposing the breast to various adipokines that produced from the adipose tissue. In a study by Wang et.al., [2019] they reported that woman with BC who is overweight/ obese had a greater risk associated with poor diagnosis in compare with BC patients who are in the normal weight range. There reason behind that is the hormonal imbalance in females that makes the breast vulnerable to tumorigenesis [50, 51]. Similarly, obesity (specially childhood obesity) was also linked to CRC [52]. In the present study, no correlations between the BMI and the age of the participants. But in other studies, it has been reported that BMI was associated age and patients had increased poor prognosis with age [53].

The present study showed a significant decrease in APN level in colorectal cancer patients compared to healthy controls among all BMI groups which is consistent with previous reports and may indicate the protective effects of APN against those cancer types [54]. Although previous reports indicated higher APN level in females compared to males, our study showed a trend toward higher APN in males and these conflicting might by resulted from the high female: male ratio included in this study (4: 1) and to the small sample size which may affect the results [55]. The decreased level of APN in obesity-related cancers over weighted patients and obese healthy controls were reported previously [56, 57].

The current study found that the most frequent genotype of *AdipoR1* rs1342387 is the homozygote GG and it is associated with cancer but no significant association was found in BC and CRC. The association of several *AdipoR1* polymorphisms with BC risk was confirmed previously [58] while the association of this polymorphism with CRC has been a debated subject, as some studies found significant association of *AdipoR1* rs1342387 polymorphism with cancer risk in the recessive heterogenetic type. Part of the reasons that cause this controversial findings is that it can be affected by factors such as ethnicity. [59]. Moreover, differences in the frequency of alleles and genotypes were also reported in different ethnicity such as Northern and Western European ancestry, and Han Chinese in Beijing [59].

The non-significance were due to the study small size of samples. As the study was started with the beginning of corona virus pandemic which made the collection of samples and ordering the kits very difficult and last for months until the curfew was ended. On the other hand this work is a part of a master program which is limited by time. Therefore, this relatively small size of samples was used.

5. CONCLUSION

This study considered to be the first to investigate APN genotypes and its association to cancer in Erbil. In addition it confirms previous studied regarding the prevalence of BC that showed superiority in compare with CRC cases.

Table 5. The article concise conclusions

Subject	Article conclusions
The study	The first study to investigate APN genotypes and its association to cancer in Erbil, Kurdistan-Iraq
Types of cancer	BC and CRC
More frequent cancer	BC is more frequent than CRC in Erbil, Kurdistan-Iraq
Sex distribution	Females were dominant in BC while males were dominant in CRC
APN levels	1. APN level decreased in obesity related cancers 2. APN levels decreased along with the increase of BMI
AdipoR1 polymorphism	1. GG is more frequent genotype in Erbil Kurdistan-Iraq population 2. The recessive AA genotype is more associated with decreased APN level

Furthermore, the dominancy of females in BC was obvious in the reported data. Moreover, the role of APN during obesity related cancer showed more decreased level than HC with decline trend along with increased BMI. The attempt to investigate the genotype of Kurdish people showed the frequency of GG genotype but the recessive AA genotype showed more effects on decreasing the level of APN despite the non-significant results (Table 5) .

ETHICS APPROVAL

Ethics approval was obtained by the ethics commission, Faculty of Science, Soran University, Erbil, Iraq. As the study was approved to be carried out with the register number 1/1N/40 in 31/10/2019.

CONSENT

As per international standard or university standard, respondents' written consent has been collected and preserved by the author(s).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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