Genomics Data 10 (2016) 118–126

Contents lists available at ScienceDirect

Genomics Data

journal homepage: www.elsevier.com/locate/gdata

Colorectal cancer and the *KIR* genes in the human genome: A meta-analysis

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ARTICLE INFO

Article history:
Received 13 September 2016
Received in revised form 21 October 2016
Accepted 30 October 2016
Available online 1 November 2016

Keywords:
Colorectal cancer
Killer cell immunoglobulin-like receptor
Meta-analysis

ABSTRACT

Colorectal cancer is one of the most common types of inflammation-based cancers and is occurred due to growth and spread of cancer cells in colon and/or rectum. Previously genetic association of cell cycle genes, both proto-oncogenes and the tumor suppressors has been proved. But there were few studies about association of immune related genes such as *killer-cell immunoglobulin-like receptors (KIRs)*. Thus we intend to perform a meta-analysis to find the association of different genes of *KIR* and susceptibility to be affected by colorectal cancer. The overall population of the four studies investigated in our meta-analysis was 953 individuals (470 individuals with colorectal cancer and 483 individuals in control groups). After the analyses, we concluded that colorectal cancer is affected by *KIR2DS5* and also there were no protecting gene. This result shows the inflammatory basis of this cancer. In other words, in contrast to leukemia and blood cancers, colorectal cancers seem to be affected by hyper activity of natural killer-cells (NKs). Whys and therefore of this paradox, is suggested to be investigated further.

1. Introduction

The most common cancer in males is the prostate [1] cancer whereas the most common cancer and malignancy in female is the breast cancer [2–5]. Among cancers, colorectal and lung cancers are of the most widespread cancers in both genders [1]. So colorectal cancer has a strategic importance for governments. Although other cancers like ovarian and endometrial cancers are also prevalent in women [6,7], but the strategic importance of colorectal cancers is higher mortality and affecting both genders.

Colorectal disease like Crohn's disease and ulcerative colitis has very strategic importance from the epidemiological points of view [8] as well as colorectal cancers. Colorectal cancer is one of the most common types of cancers, particularly in developed countries and it is defined as growth and spread of cancer cells in colon or rectum [9]. This disease usually has no specific symptom and often diagnose in latest and dangerous stages of the disease. Most important symptoms are blood existence in stool, weight loss and permanent fatigue [10,11]. The cause of getting this cancer is related to lifestyle, age and gender (men will getting this cancer more than women) because of obesity, alcohol consumption, high consumption of red meat, absence of fibers in diet, physical inactivity and especially tobacco abuse [12–14]. Increasing age also has a significant impact on the risk of this cancer so that a lot of people over 70 years of age in Western societies gett adenoma and adenoma increases the possibility of getting this cancer [15,16]. This disease has several stages. In the first stage, cancer cells are in inner layer of colon or rectum, in the next stage the cancer spreads in muscular layer of colon or rectum, thereafter in a next stage, the cancer enter to a few lymph nodes in the same area and after that in another stage metastasis occurs and the cancer spreads into other tissues and body areas; at this stage the disease is usually not curable [17–19]. Most colorectal cancers originate from the benign adenomas that forms in colon. Molecular and genetic studies indicate that about 70% of colorectal cancers arise by mutation and inactivation of the gene *adenomatous polyposis coli* (*APC*) and other tumors arising as a result of activating mutations in the genes that producing beta-catenin and axin [16,20–22]. Also other genetic studies have shown that this cancer usually arises due to the mutations that cause instability of some chromosomes and change the structure of these chromosomes. These chromosomal changes cause not to produce an enough number of copies of the tumor suppressors like *APC* and *P53* [23–28]. Other than tumor suppressor genes, this and some other cancers can be affected by proto-oncogenes like *the ubiquitin-like with PHD and ring-finger domains 1* (*UHRF1*) [29]. Other researches have indicated that mutation in *KRAS* and epidermal growth factor (EGF) signaling pathways have an important role in getting this cancer [30,31].

Immune system responses have important role in controlling and preventing development of colorectal cancers [26]. Colorectal cancer

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http://dx.doi.org/10.1016/j.gdata.2016.10.010

Table 1
KIR genes. KIR has 14 discovered genes and 2 discovered pseudo-genes. Seven number of them are inhibitory, 1 of them is both inhibitory and activating and 6 number them are activating. Each gene has different alleles; So KIR is highly polymorphic like HLA.

KIR genes															
Inhibitory KIRs								Activating KIRs						Pseudo genes	
2DL1	2DL2	2DL3	2DL4	2DL5	3DL1	3DL2	3DL3	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	2DP1	3DP1

cells have several antigens which recognized by immune system. Among these antigens, Carcinoembryonic antigen (CEA) is the most studied [32,33]. In addition, several neo-antigens were detected in these tumor cells. These neo-antigens are the cause of high levels of lymphocytes infiltrating to the tumor cells [23]; so the cancer progression can be diagnosed from the level of lymphocyte infiltration. Since generally the cancerous cells fail to express human leukocyte antigen (HLA) class I and therefore bypass cytotoxic T lymphocytes, natural killer-cells (NKs) as important components of the innate immune system, play a key role in this condition [34]. Killer cell immunoglobulin-like receptors (KIRs) (also called as CD158) are polymorphic glycoproteins expressed on cell surface of NKs and T cell subsets [35]. *KIR* gene family is highly polymorphic and its genomic diversity is achieved through differences in gene content as well as allelic polymorphism [36,37]. Of course the most polymorphic loci in human genome is *HLA* [38] which the molecules of its, are in direct contact with KIR molecules. Hereby we intend to investigate the role of the *KIR* genes in colorectal cancer as a meta-analysis to find the association of different genes of *KIR* and susceptibility to be affected by colorectal cancer.

2. Material and methods

The present study is a meta-analysis which approximately covers all the original studies on this topic done before. We searched in databases such as google scholar, science direct and Pubmed. Totally six papers were found that four of them had same protocols.

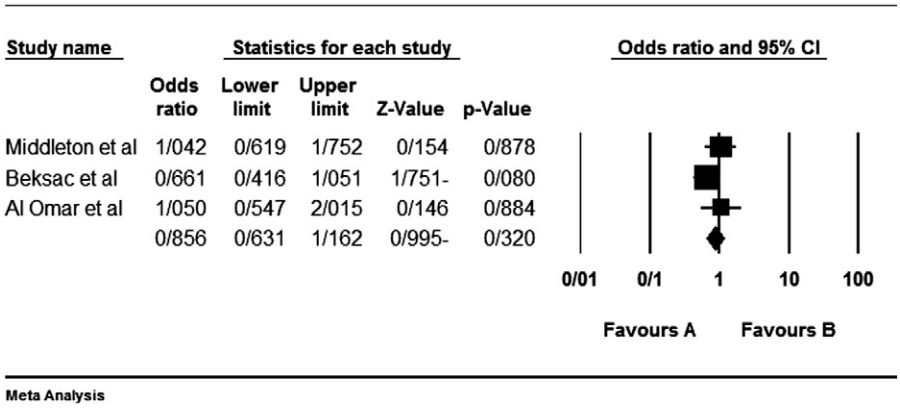

Fig. 1. Colorectal cancer is not statistically affected or protected by the *KIR2DL1*. Left side (the favours A) shows protecting effect in all figures.

Table 2
Data and meta-analysis. The ED stands for effective direction and the nagative and possitive each one respectively means protective effect and risk factor.

Gene	Middleton et al. [58]		Beksac et al. [60]		Al Omar et al. [61]		Kim et al. [57]		Meta-analysis
	Cancer N = 90	Control N = 100	Cancer N = 87	Control N = 154	Cancer N = 52	Control N = 70	Cancer N = 241	Control N = 159	*P* value (ED)
2DL1	86	94	77	147	51	70	241	159	0.32 (−)
2DL2	61	57	68	103	47	55	27	20	0.07 (+)
2DL3	69	85			48	56	240	159	0.99 (+)
2DL4					52	70	241	159	Excluded
2DL5	50	52			45	53	107	59	0.09 (+)
3DL1	83	91			51	66	229	156	0.45 (−)
3DL2					52	70	241	159	Excluded
3DL3					50	70	241	159	Excluded
2DS1	36	39	40	75	43	25	106	56	0.28
2DS2	61	58	54	103	46	50	31	31	0.09 (−)
2DS3	29	34	34	52	40	40	32	29	0.81 (+)
2DS4	82	91			51	70	229	156	0.41 (−)
2DS5	34	26			35	22	80	33	0.0001(+)****
3DS1	34	39	35	76	43	16	99	56	0.18 (+)
2DP1					52	70	241	159	Excluded
3DP1					52	70	241	159	Excluded

**** Significance at $P < 0.05$ level.

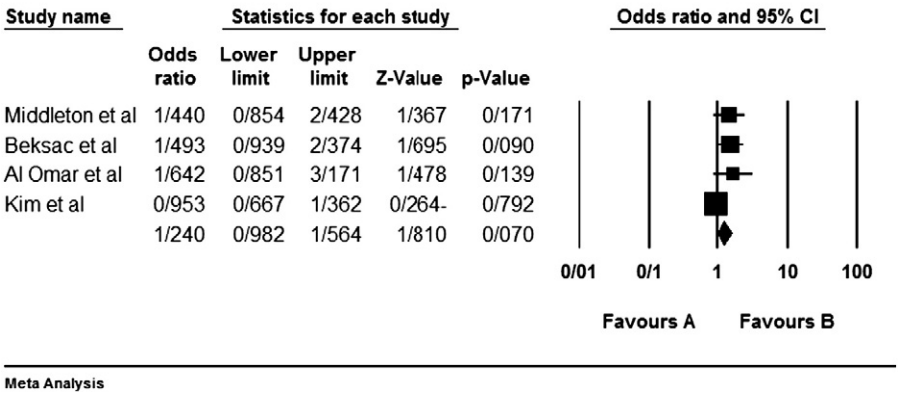

Fig. 2. Colorectal cancer is not statistically affected or protected by the *KIR2DL2*.

The overall population of this four studies consists of 953 individuals (470 individuals with colorectal cancer and 483 individuals in control groups). The test chi-squared 2 multiplied by 2 with Yate's correction was used to assay each gene separately. Then the results were imported into the software comprehensive meta-analysis version 2. The 5 genes *2DL4*, *3DL2*, *3DL3*, *2DP1* and *3DP1* were excluded from test because of their persistence in all participants of the both groups.

3. Results

3.1. About KIR

Depending on the number of extracellular immunoglobulin domains, KIRs are divided into two distinct groups (2D or 3D). Two types of KIR, i.e. inhibitory and activating, have been distinguished based on length of the intracellular domain. Inhibitory KIRs (iKIRs) are characterized by a long intra-cytoplasmic tail (denoted by an 'L' in their name) and presence of at least one immunoreceptor tyrosine-based inhibitory motif (ITIM). Activating KIR (aKIR) are characterized by a short intra-cytoplasmic tail (denoted by an 'S' in their name) and the absence of ITIM [37].

Up to now, fourteen distinct types of KIR have been identified in the human genome [39]. NKs are a subset of lymphocytes comprising around 10–15% of total lymphocytes in peripheral blood [40]. NKs principally contribute to innate immunity and also adaptive immune responses by killing the targeted cells of theirs and production of a variety of cytokines and chemokines [37]. Overall, upon interaction with their ligands which are usually HLA class I, KIR provide inhibitory

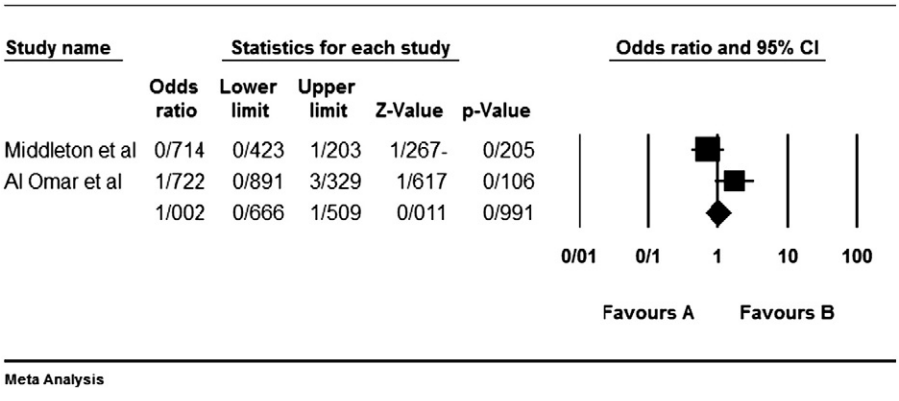

Fig. 3. Colorectal cancer is not statistically affected or protected by the *KIR2DL3*.

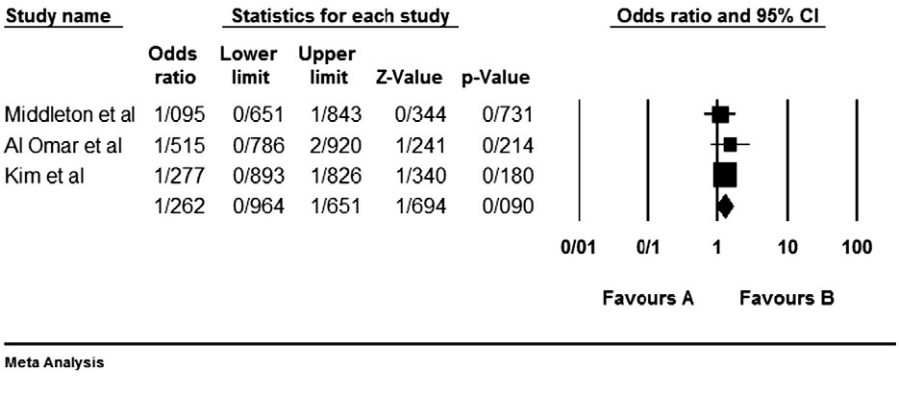

Fig. 4. Colorectal cancer is not statistically affected or protected by the *KIR2DL5*.

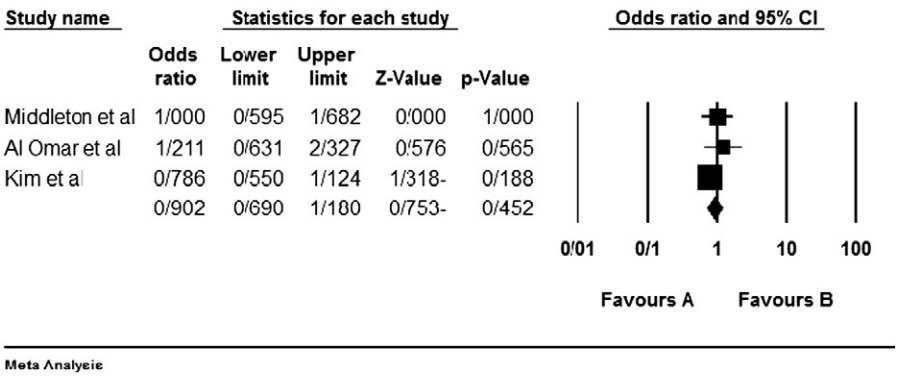

Fig. 5. Colorectal cancer is not statistically affected or protected by the *KIR3DL1*.

or activating signals to regulate the activity of NKs, which contributes to pathogenesis of diverse kinds of diseases [41,42]. Different compounds of KIR-HLA genotypes can induce different thresholds of activation in NK family and such genotypic variations have been found to be associated with a number of human diseases and complications including viral infections, autoimmune disorders and cancers [43] as well as reproduction abnormalities [44,45]. The *KIR* gene cluster on chromosome 19q13.4 within the leukocyte receptor complex (LRC) consists of a centromeric and telomeric region [46]. So far, 14 *KIR* genes and 2 pseudogenes have been described [47] (Table 1). Seven genes of *KIR3DL1-3*, *KIR2DL1-3* and *KIR2DL5* encode for the inhibitory KIR (iKIR), six genes of *KIR3DS1* and *KIR2DS1-5* encode for activating KIRs (aKIR), one gene encodes for KIR2DL4 with both inhibitory and activating functions, but more of inhibitory, and two genes of *KIR2DP1* and *KIR3DP1* are pseudogenes that do not encode a functional KIR molecule [47].

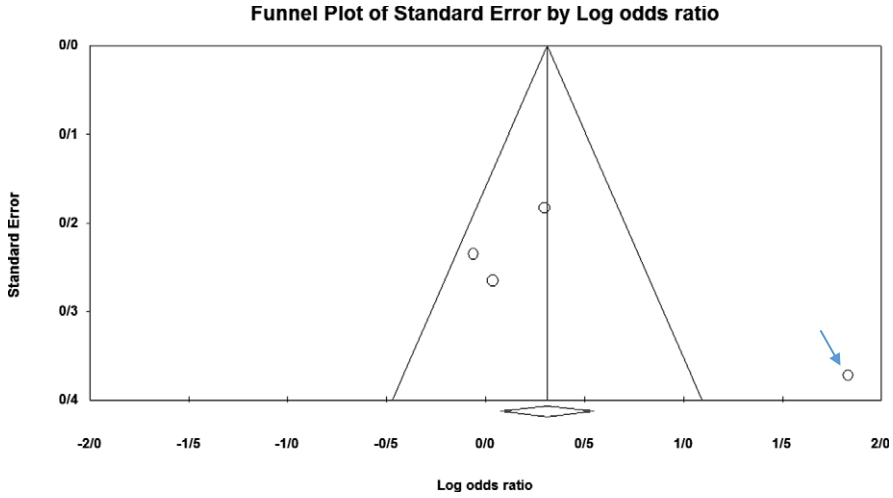

Fig. 6. *KIR2DS1*. The arrowed population in for the study of Al Omar et al.

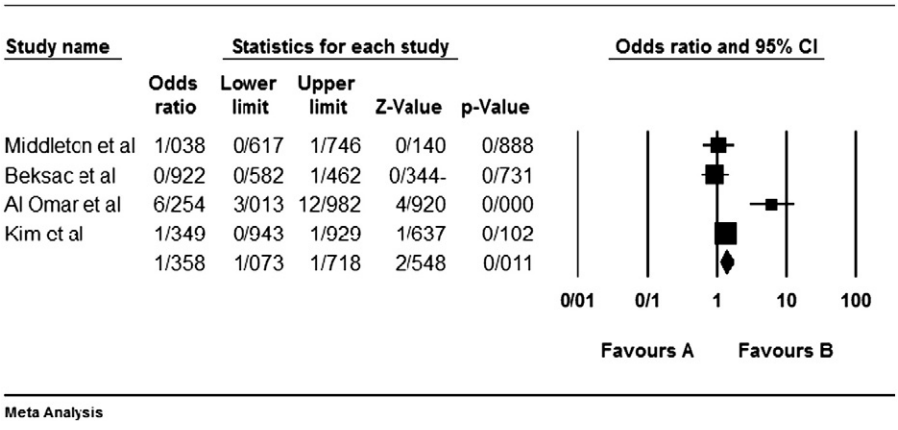

Fig. 7. *KIR2DS1* meta-graph, before exclusion of Al Omar's et al. study.

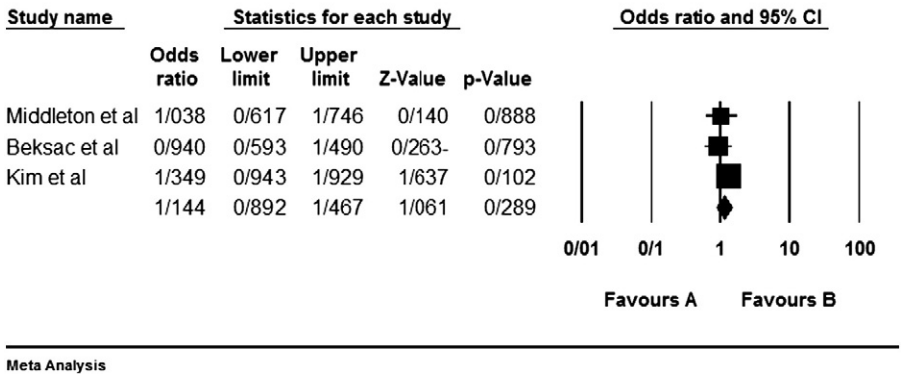

Fig. 8. *KIR2DS1* meta-graph, after exclusion of Al Omar's et al. study.

About NK subsets, we have mainly $CD16^{+}CD56^{dim}$ and $CD16^{-}$-$CD56^{bright}$; the dim form has more cytotoxic capacity called as "cytotoxic NK" and the bright form contributes in secretion of inflammatory cytokines called as "immune-regulatory NK". Both of them express KIR, but the dim form express more. [35,37,44,46,48–52].

The KIR gene cluster is flanked by *KIR3DL3* at centromeric end and *KIR3DL2* at telomeric end; both of which are present on virtually all haplotypes. Two groups of KIR haplotypes have been defined on the basis of gene content and are termed as haplotypes A and B. The A haplotypes are uniform in terms of gene content and the most prevalent form of them is composed of five inhibitory genes (*KIR2DL1*, *2DL3*, *3DL1*, *3DL2* and *3DL3*), one activating gene (*KIR2DS4*), and the *KIR2DL4* which may have both inhibitory and activating capacity. Interestingly, many A haplotypes possess null variants of both *KIR2DS4* and *KIR2DL4* that are not expressed on the cell surface. Thus these haplotypes technically possess no functional aKIR gene. The B haplotypes contain variable numbers of activating and inhibitory genes and are the primary contributors to the extraordinary differences in KIR gene profiles observed in distinct ethnic populations across the world. The interaction of inhibitory KIR with HLA class I as their ligands, triggers the signals that turn off

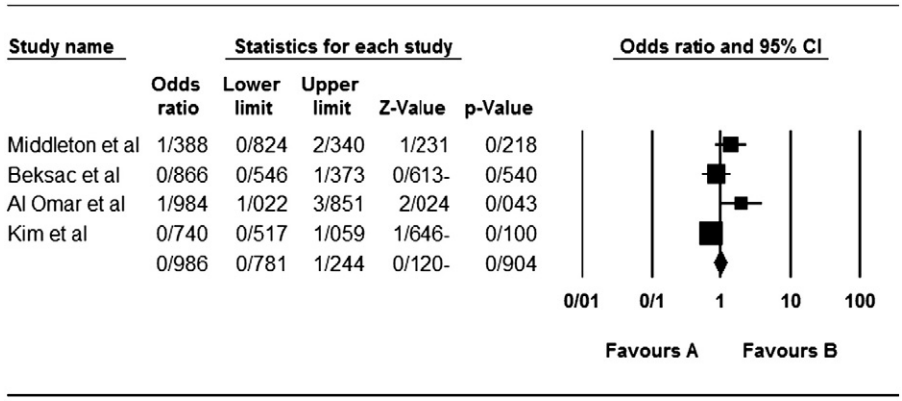

Fig. 9. Colorectal cancer is not statistically affected or protected by the *KIR2DS2*.

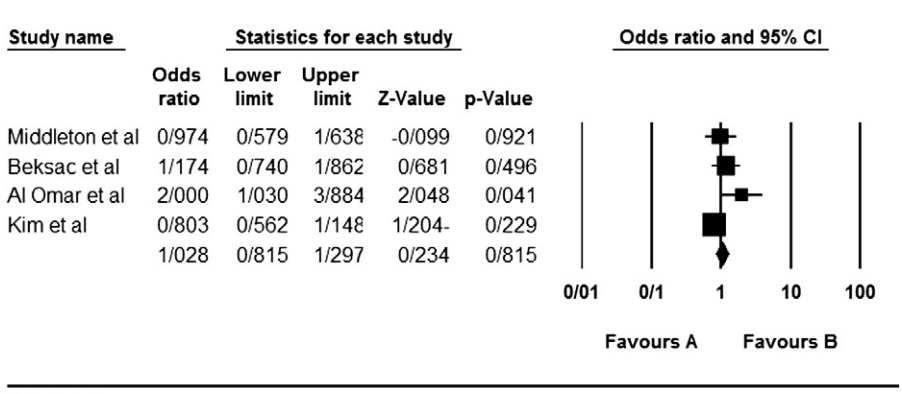

Fig. 10. Colorectal cancer is not statistically affected or protected by the *KIR2DS3*.

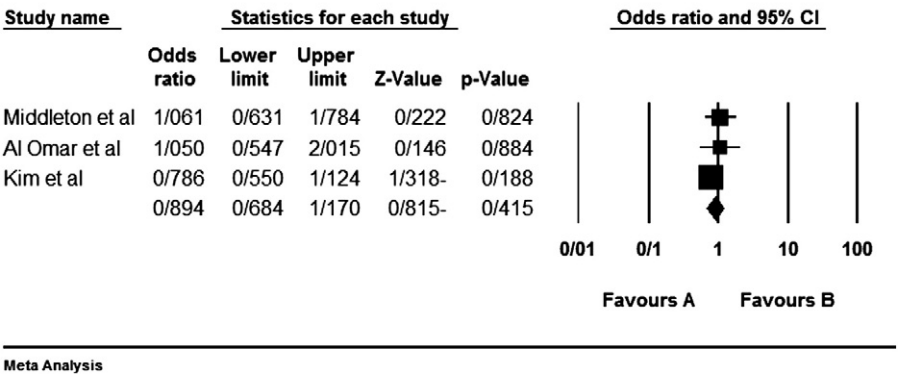

Fig. 11. Colorectal cancer is not statistically affected or protected by the *KIR2DS4*.

the NKs. Therefore, by expressing HLA-A, -B and -C molecules, healthy cells are protected against NK lysis. Down-regulation of HLA class I expression due to tumor transformation or viral infection permits NKs to lyse these unhealthy targeted cells of theirs, a phenomenon first described as the "missing-self" hypothesis. Thus the compound KIR-HLA genotypes that lead to lower inhibition and higher activation appear to be beneficial in resistance to viral infections and cancers. On the other hand, these dominant activating genotypes may constitute a risk for susceptibility to autoimmune and inflammatory diseases [43].

3.2 KIR and colorectal cancer

As a general rule NKs play a key role against the cancerous cells escaped from toxic activity of T cells. So the KIRs expressed on surface of NKs become important. We know that the interaction KIR-HLA has two sides of KIR and HLA. For example overexpression of HLA-E on surface of colorectal cancer cells can result in inhibition of NKs [53] and such patients have better survival from the disease [54]; of course the receptor of HLA-E is CD94/NKG2a [55,56]. KIR2DL1 and 2DS1 interact

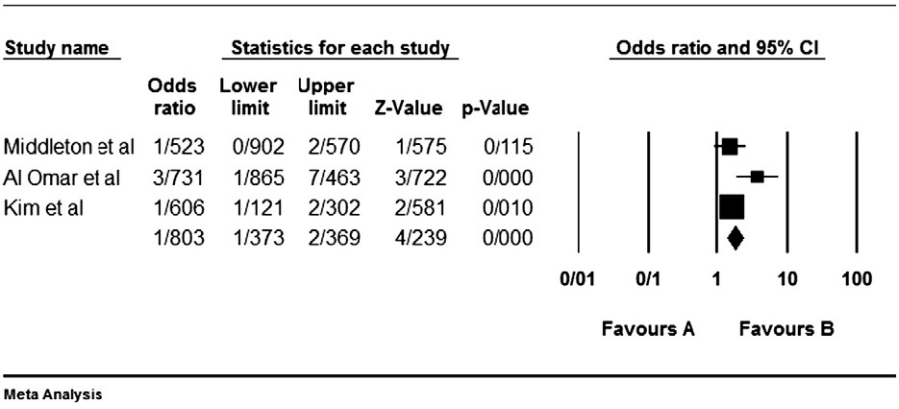

Fig. 12. *KIR2DS5 meta-graph*. Even with exclusion of the study of Al Omar's et al., the *P* value would be as 0.003. For this gene, the mentioned study did not have an odds ratio bias.

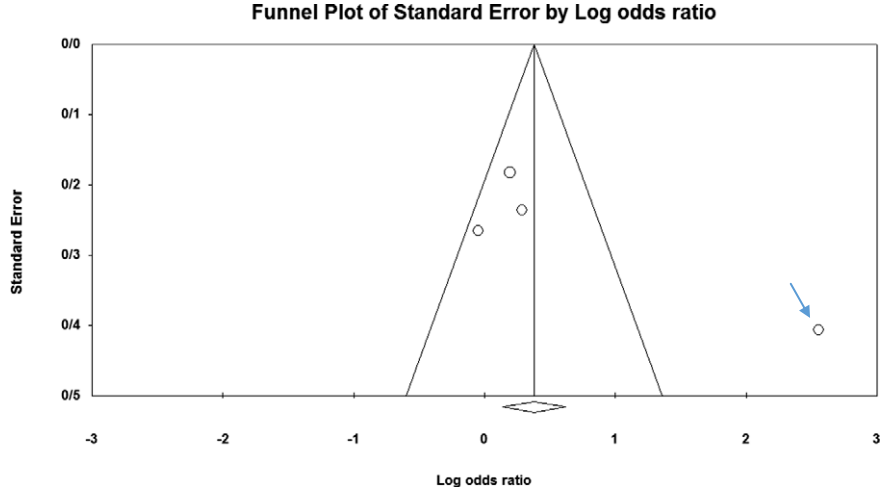

Fig. 13. *KIR3DS1* and that study of Al Omar's et al.

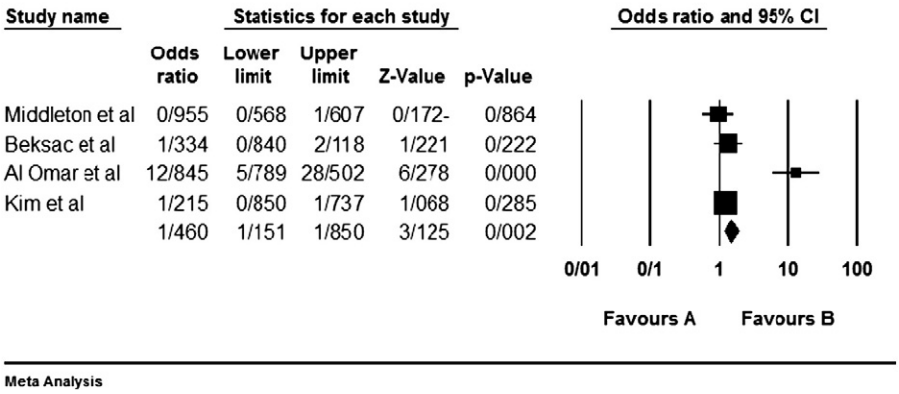

Fig. 14. *KIR3DS1* meta-graph, before exclusion of Al Omar's et al study.

with HLA-C2, and KIR2DL2, 2DL3 and 2DS2 interact with HLA-C1 [57]; so every mathematical predict do not occur. Although at the first glance it seems that inhibitory types of each or both sides may be associated with the more susceptibility, but this rule is not true for such inflammation-based cancers. The whys and therefore of this paradox, is not clear; however there are some good data in study of Middleton et al. [58] about loss of HLA expression in colorectal cancer cells giving us insight. Also role of allograft inflammatory factor 1 (Alf1) shows the inflammation base of this disease [59].

Although the most inhibitory effect is attributed to the interaction KIR2DL1-HLA-C2 [57], but none of our analyzed studies do not show any significant protective effect. Of course we reanalyzed previous articles' data with Yate's correction; so the relation of some genes in some studies were significant in the study of theirs without Yate's correction. For example Beksac et al. [60] had been found a significant protective effect for *KIR2DL1* as we did not found so (Fig. 1).

Among the four studies analyzed by us (Table 2), the three genes *2DL4*, *3DL2* and *3DL3*, and both pseudogenes were present in approximately all participants of the studies, so these genes were excluded from our meta-analyses. Among the other genes, at first, the meta-analyses showed a significant association for the genes *2DS1*, *3DS1* and *2DS5* (Figs. 1–15); but because of high odds ratio of study of Al Omar et al. in Saudi Arabia [61] for the genes *2DS1* and *3DS1* (Figs. 6, 13), we were supposed to exclude it from the analysis of these two genes. After the exclusion, only association of *KIR2DS5* remained significant (Figs. 7, 8, 12, 14, 15).

Another justification for this paradox is different basis of different cancers. As we published before, breast cancer is affected by *KIR2DL2* which is an inhibitory gene [62]. In verse, colorectal cancer is affected by an activating KIR as we found in the present meta-analysis. Although at the first glance it seems that inhibitory interactions of KIR-HLA may be associated with the more susceptibility to colorectal cancer because of this fact that NKs play a key role against the cancerous cells escaped from toxic activity of T cells because of their loss of HLA expression, but this rule is not true for such inflammation-based cancers.

Other than the justification above, another justification is that the ligands of activating KIRs are not necessarily HLAs; rather, they are still unknown [36,53]. This, can be pointed out as the limitation of the previous studies.

4. Conclusion

Finally we concluded that colorectal cancer is affected by *KIR2DS5* and also there were no protecting gene. This result shows the inflammatory basis of this cancer. In other words, in contrast to leukemia and blood cancers, colorectal cancers seem to be affected by hyper activity of natural killer-cells (NKs). Whys and therefore of this paradox, is suggested to be investigated further.

Conflict of interest

We declare that there is no conflict of interest.

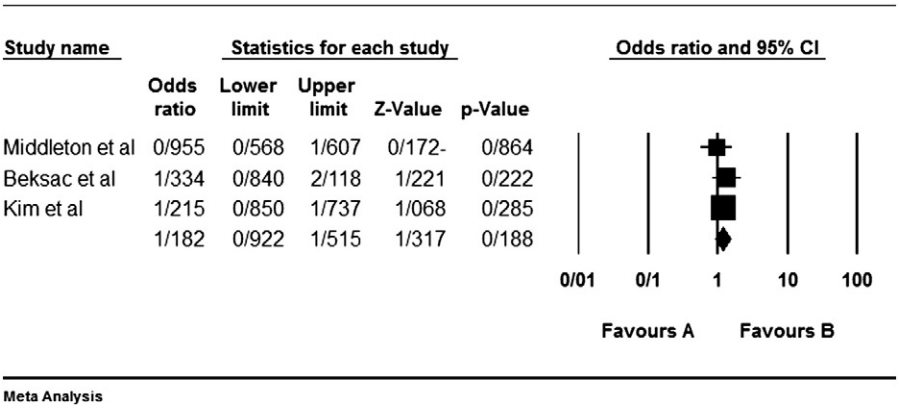

Fig. 15. *KIR3DS1* meta-graph, after exclusion of Al Omar's et al study.

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