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The correlations between IL-17 versus Th17 cells and cancer patient survival: a systematic review

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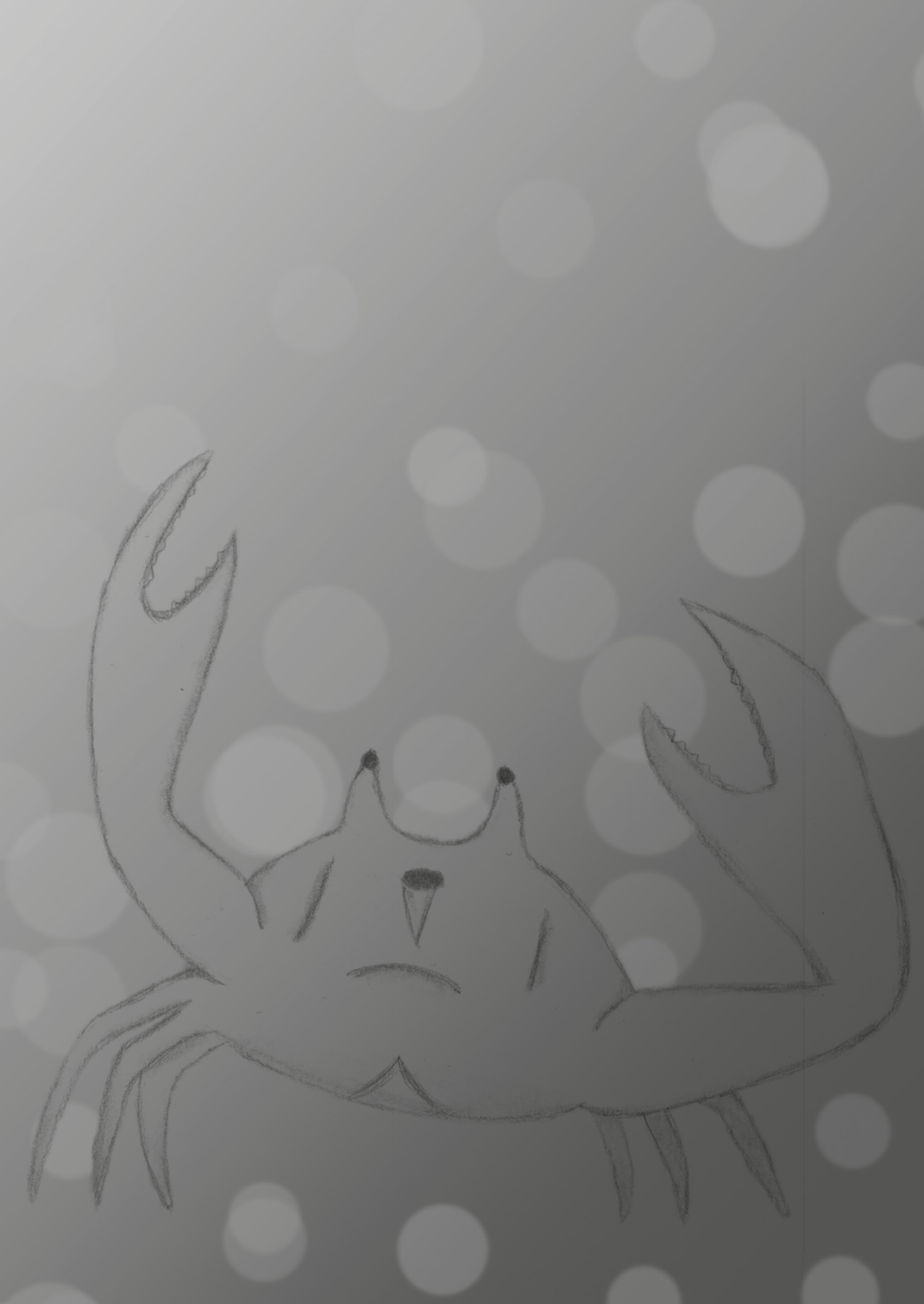


Abstract

Both IL-17 and Th17 cells have been ascribed tumor promoting as well as tumor suppressing functions. We reviewed the literature on correlations between IL-17 versus Th17 and survival in human cancer, following the PRISMA guidelines. Serum, formalin fixed paraffin embedded tissue and peripheral blood samples were most frequently studied. High IL-17 quantities were correlated with poor prognosis, whereas high Th17 cell frequencies were correlated with improved prognosis. Since Th17 cells are a subpopulation of IL-17$^+$ cells and had a different correlation with prognosis than total IL-17, we substantiate that a distinction should be made between Th17 and other IL-17$^+$ cells.

Introduction

Interleukin-17 (IL-17) was discovered in 1993 and originally named cytotoxic T lymphocyte-associated-8 (CTLA-8).[1] IL-17 was more recently renamed IL-17A and has five family members: IL-17B-F.[2] Only IL-17F shows some homology and overlapping functions with IL-17A. The main functions of IL-17 are the attraction of neutrophils and stimulation of inflammation.[3] The T helper 17 (Th17) cell, one of the predominant producers of IL-17 that was characterized in 2005,[4] is essential to protect the host against pathogens that are not handled well by Th1 and Th2 cells.[5] This pro-inflammatory cell type plays a dominant role in a variety of autoimmune diseases.[3] Antibodies targeting IL-17 and its receptor are now used in clinical trials to treat autoimmune diseases like psoriasis, rheumatoid arthritis and Crohn's disease.[6] Since IL-17 can also be produced by innate immune cell types including both lymphoid derived (e.g. γδT cells, invariant natural killer T cells and innate lymphoid cells)[7,8] and myeloid derived cells (e.g. neutrophils, macrophages and mast cells),[9] it may bridge the activities of the innate and adaptive immune system.[10]

Much less studied is the role of IL-17 in cancer. Both tumor suppressing and tumor promoting functions have been ascribed to the IL-17 protein and Th17 cells.[11] This ambiguity about the function of IL-17 and Th17 cells in cancer has limited the potential for targeting the molecule or using cell-based immunotherapy. Part of the ambiguity may have arisen because different aspects of the IL-17 response are studied. Total protein amount or cells expressing IL-17 protein have been measured in serum and tumor associated fluids by ELISA and in formalin-fixed, paraffin-embedded (FFPE) tissue by immunohistochemistry, respectively. The effect of Th17 cells has been analyzed mainly in peripheral blood, but also in tumor associated fluids, FFPE and fresh frozen tissue by flow cytometry, immunohistochemistry or RT-PCR. A review on Th17 cells in cancer by Wilke *et al*. in 2011 already noted that correlations between the IL-17 protein and survival may be different from correlations with the Th17 cell population.[12]

To systematically study the correlations between the IL-17 protein and Th17 cells and survival in human cancer, we investigated all publications in NCBI PubMed, Ovid Embase and Web of Science addressing this subject. The aim of our study was to identify the correlations between both IL-17 protein and Th17 cells and prognosis in cancer. The studies were classified by the sample type used to study IL-17 or Th17 cells: serum, FFPE tissue, peripheral blood, tumor associated fluids and fresh frozen tissue. Subsequently, the effect on survival was analyzed for each of the sample types studied. The implications for further research of IL-17 and Th17 cells are discussed.

Results

Study design and selection criteria

Of the 2643 publications identified through database searching on IL-17 or Th17 and cancer, 56 studies met the inclusion criteria (Figure 1). The main reasons for a publication to be excluded were: being a conference abstract (23%), an animal study (24%), no study on cancer (27%) or not reporting on survival data (19%). Two articles were excluded due to lack of other references on the same method and survival analysis. One article reported on an IL-17 SNP analysis,[13] while the other studied RNA levels of Th17 cell expressed retinoic acid receptor-related orphan receptor gamma (RORγt).[14] Neither of these studies found a correlation with survival. An overview of the included studies sorted by sample type and clinical outcome is shown in Table 1.

Studies reporting on survival analysis or risk of recurrence were included regardless of the outcome of the study. A potential publication bias was caused by excluding articles that reported on correlations with other clinico-pathological parameters but not survival. This bias was minimized by screening all articles that reported on correlations with clinico-pathological parameters for having performed a survival analysis. The survival criterion enabled us to focus on studies that are relevant for the potential targeting of IL-17 or Th17 cells in a clinical setting.

Generally, a random or consecutive group of patients was analyzed for relatively objective measures (see supplementary Tables S1-4). Although most studies did not provide details on the sample selection method, the majority of the studies used as a continuous variable or categorized IL-17 or Th17 cell numbers in groups based on the presence, mean or median to analyze the effect by Kaplan-Meier and Cox regression analyses. Potential risks of bias identified in categorizing IL-17 or Th17 expression were optimal cut-off values chosen arbitrarily[15,16] or using a minimum p value,[17-23] ROC curve[24-27] or regression tree analysis.[28] Furthermore, one study compared the six long (>3 years) versus short (<1.5 years) surviving patients.[29] Another study reported that post-chemotherapy samples were used when no pretreatment samples were available for immunohistochemistry.[30] A final potential risk factor was observed in a study of leukemia patients treated with allogeneic stem cell transplantation after myeloablative

conditioning, which included donors that varied from related to unrelated and different prophylaxis regimens to prevent graft-versus-host disease.[31] Additional study details and concerns are listed per sample type in supplementary Tables S1-4. Clinico-pathological characteristics of the different studies per measurement method are provided in supplementary Tables S5-8.

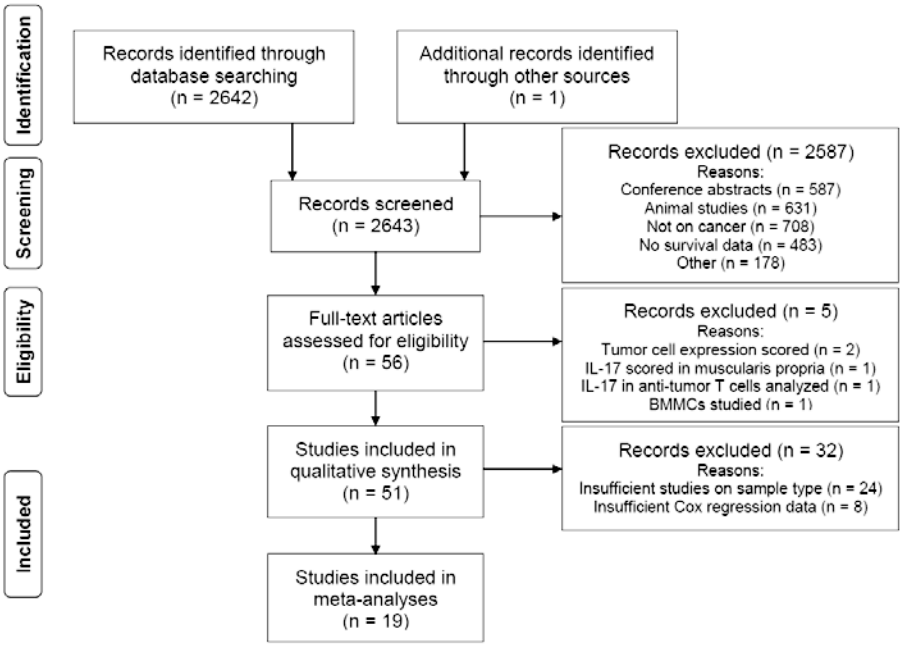


Figure 1. PRISMA Flow diagram

Database searching identified 2642 publications on IL-17 or Th17 and cancer. One publication on this topic of our group published in this issue of OncoImmunology was added manually. Using the search term 'tumor' caused studies on tumor-necrosis factor to be selected regardless of whether the study was on cancer. Although tumor necrosis factor was excluded as a major topic, many publications that were not on cancer had to be excluded manually. All inclusion criteria were met by 56 articles. Five studies were excluded from analysis for using different sample types or methods than all other articles. Another 32 studies were excluded from meta-analysis because not enough studies were available on sample types other than tissue analyzed for IL-17 expression or insufficient data were provided. Figure adapted from Moher et al.[80]

High IL-17 serum levels are correlated with poor survival

Serum, paraffin tissue, peripheral blood mononuclear cells (PBMCs) and occasionally tumor associated fluids or fresh frozen tissue were used to measure IL-17 protein or RNA and Th17 cells. Since the cell source and related activity measured may differ in different sample types, we sorted and analyzed the studies by sample type. The amount of IL-17 protein in serum was measured by ELISA (Table 1.1). Since total protein quantity was measured, the IL-17 could have been derived from Th17 cells but also from innate immune cell types. Five studies out of ten reported that a high amount of serum IL-17 protein was correlated with poor survival.[17,24-26,31] One study showed a

correlation between a high IL-17 level and improved survival in leukemia.[32] Four studies did not observe a significant correlation between high serum IL-17 levels and survival,[33-36] although one group did find a trend toward poor prognosis (p=0.05).[36] Overall, a high amount of IL-17 protein in serum has predominantly been correlated with poor survival (Table 2).

Table 1.1. Correlation between IL-17 in serum and survival

Cancer type	N	Outcome	Correlation	Multivariate Cox p<0.05	Notes	Ref #
NSCLC	128	OS	Poor	Yes		25
HBV-related HCC	105	OS, DFS	Poor	DFS: Yes OS: NA		26
Leukemia treated with myelo-ablative conditioning and SCT	95	DFS	Poor	Yes		31
Gastric carcinoma	85	OS	Poor	Yes		17
CRC	80	DFS	Poor	NA		24
Acute leukemia	93	OS	Improved	No		32
CLL	294	OS	No correlation		sample type: plasma	33
CLL	84	OS	No correlation			34
Pancreatic AC	62	OS	Trend toward poor			36
Multiple myeloma	50	OS	No correlation		peripheral blood, bone marrow	35

Table 1.2. Correlation between IL-17$^+$ cells in tissue and survival

Cancer type	N	Outcome	Correlation	Multivariate Cox p<0.05	Notes	Ref #
HCC	323	OS, DFS	Poor	No		40
HCC	300	OS, DFS	Poor (intratumoral)	NA		18
HCC	150	OS, DFS	Poor (intratumoral)	No	peritumoral IL-17$^+$ cells correlated with improved survival	41

HCC	108	OS, DFS	Poor (intratumoral)	Yes	hot-spot areas scored	19
HCC	56	OS, DFS	Poor DFS	NA	both intra- and peritumoral cells scored	42
HCC	43	OS, DFS	Poor	Yes		43
Intrahepatic cholangiocarcinoma	123	OS	Poor (intratumoral)	Yes		44
CRC	104	DFS	Poor	NA	both tumor center and invasive margin scored	20
CRC	102	OS	Poor	NA		45
CRC	52	OS	Poor	Yes		16
NSCLC	102	OS	Poor	NA		46
NSCLC	52	OS, DFS	Poor	Yes	same research group as ref 16	15
Breast carcinoma	207	OS, DFS	Poor DFS	Yes	scores in tumor center and front hot-spots averaged	30
Gastric carcinoma	112	OS	Poor	Yes	mainly mast cells were IL-17^{+}	50
Cervical SCC	109	OS	Poor (TNM stage I)	Yes	NS in all TNM stages	37
Gallbladder carcinoma	104	OS, DFS	Poor OS	No		47
Laryngeal SCC	71	DFS	Poor	No		49
Pancreatic AC	46	OS	Poor	NA	condensed expression areas scored	48
Gastric AC	192	OS	Improved	Yes		51
Esophageal SCC	181	OS	Improved	No		52
Cervical carcinoma	153	DFS	Improved	Yes	densest lymphocytic infiltrates scored	21
Recurrent ovarian carcinoma	47	OS, DFS	Improved DFS	No		28

Pancreatic ductal AC treated with vaccine, CT, RT	12	OS	Improved	NA	lymphoid aggregates scored	29
HCC	132	OS, DFS	No correlation		densest lymphocytic infiltrates scored	22
Nasopharyngeal carcinoma	106	OS	No correlation			53
Epithelial ovarian carcinoma	104	OS	No correlation		consecutive hot-spot areas scored	23
Giant cell tumors of bone	74	DFS	No correlation			54
Esophageal SCC	215	OS	High IL-17$^+$ cells in tumor muscul. propria correlated with improved OS	Yes	correlation between IL-17$^+$ cells in tumor nests and survival not studied	39*
CRC	78	OS, DFS	Improved	Yes	mainly tumor cells positive	55*
Stage IV glioblastoma	41	OS	Improved	Yes	mainly tumor cells positive	56*

Table 1.3. Correlation between Th17 cells and survival

Cancer type	Sample	N	Measurement	Outcome	Correlation	Multivariate Cox p<0.05	Notes	Ref #
Cervical SCC	FFPE	51	IHC CD3$^+$ IL-17$^+$ cells	OS	Improved	Yes		37
Diff. thyroid carcinoma	FFPE	266	IHC CD4$^+$ IL-17$^+$ cells	DFS	Trend toward improved			59
HCC	PBMC	150	FC CD4$^+$ IL-17$^+$	DFS, OS	Poor	Yes		41
Gastric carcinoma	PBMC + PMA/iono/ mon 4u	32	FC CD4$^+$ IL-17$^+$IFNG$^-$	OS	Poor	NA		62

Acute leukemia	PBMC + PMA/iono/ mon 5h	93	FC $CD3^+CD4^+$ $IL\text{-}17^+$ cells	OS	Improved	Yes		32
CLL	PBMC + 5h PMA/iono/ mon	66	FC $CD3^+CD4^+$ $IL\text{-}17^+$ cells	OS	Improved	No	Same group: ref 34	38
End-stage melanoma treated with aCTLA4	PBMC + 2.5h PMA/iono/ 2h mon	47	FC $CD4^+CD8^-$ $IL\text{-}17^+$ increase 6m after/1wk before therapy	DFS	Improved	NA		61
HCC treated with transarterial chemoem-bolization	PBMC + activation mix at -5h and +30d	30	FC $CD4^+$ $IL\text{-}17^+$ cells	OS	Improved (+30d measurement)	Yes	NS for -5h mea-sure-ment	60
CLL	PBMC + PMA/iono/ mon 5h	150	FC $CD3^+CD4^+$ $IL\text{-}17^+$ cells	OS	No correlation			33
Hematologic melagnancy treated with allogeneic HSCT	PBMC	30	FC $CD3^+CD4^+$ $CD8^-IL\text{-}17^+$ cells	DFS	No correlation	NA	60% of patient got GVHD	64
HCC	PBMC	26	FC $CD4^+$ $IL\text{-}17^+$ cells	DFS	No correlation		IL-17 ELISA <detect limit	63
Stage IV melanoma with anti-tumor antigen T cell response	Melan-A reactive $CD3^+CD4^+$ PBMC + 12d peptide mix + 12h antigen/mon	38	FC IL-17 present/absent	OS	Poor	Yes	IL-17 present in n=3; CD4 related with poor OS	65*
Acute myeloid leukemia	BMMC + 5h PMA/iono /bref	98	FC $CD3^+CD8\text{-}$ $IL17^+$	OS	Poor	NA	no corr. for PBMC (n=30)	66*
CRC	normal biopsies ~10cm from tumor center	19	qRT-PCR IL-17	OS	No correlation			57

Ovarian carcinoma	fresh frozen tumor tissue	17	agarose gel RT-PCR IL-17 present	OS	No correlation			58

Table 1.4. Correlation between IL-17 and Th17 cells in tumor associated fluids and survival

Cancer type	Sample	N	Measurement	Outcome	Correlation	Multivariate Cox p<0.05	Notes	Ref #
Lung carcinoma	MPE supernatant	78	ELISA IL-17	OS	Poor	Yes		27
Ovarian carcinoma	tumor ascites	85	ELISA IL-17	OS	Improved	Yes		69
Lung carcinoma	MPE	30	FC $CD4^+$ $IL\text{-}17^+$ cells	OS	Improved	Yes		67
Lung AC with pleura metastasis	MPE +2h PMA/iono +4h Bref/mon	24	FC $CD3^+CD4^+$ $IL\text{-}17^+$ cells	OS	Improved	NA		68
Gastric carcinoma	peritoneal lavage	114	qRT-PCR IL-17	OS	Improved (curative resections; n=79)	Yes	NS for all patients (n=114)	70

Table 1. Correlation between IL-17 or Th17 and survival

All studies describing a correlation between a measurement of IL-17 or Th17 cells and overall or disease-free survival are shown. The analyses were sorted by clinical outcome, cancer type and study size. N indicates the number of patients on which the correlation between the IL-17 measurement and survival was reported. The column 'Correlation' indicates whether a high IL-17 or Th17 cell measurement was correlated with poor or improved survival. If this correlation was significant under a certain condition (e.g. for OS or DFS only, or for a scoring location), this is also indicated. A dark grey row indicates a correlation with poor survival, a white row a correlation with improved survival and a light grey row no significant correlation. Whether or not the correlation found was independently correlated with survival when corrected for clinico-pathological parameters in a multivariate Cox regression analysis is also indicated. A multivariate analysis including both the IL-17 measurement as well as another variable also containing this IL-17 measurement (e.g. a ratio) was not included in our analysis since the potential effect might be lost by correcting for it. Measurement deviances are indicated under 'Notes'. Only if a study on a certain cancer type was performed by the same research group as another included study, a note is included because of potential sample overlap. An asterisk behind a reference number indicates that the study was not included in the quantitative analyses in Table 2 and Figure 2. Table 1.1 shows analyses on IL-17 quantifications in serum by ELISA. Table 1.2 is a representation of studies on tumor infiltrated IL-17+ cells quantified by immunohistochemistry on FFPE tissue slides or tissue microarrays. If 'intratumoral' is indicated, peritumoral cells were scored as well. Table 1.3 shows analyses of Th17 quantification on FFPE tissue, peripheral blood PBMCs and fresh frozen samples. Table 1.4 represents the analyses on tumor associated fluids sorted by measurement type. Abbreviations: AC=adenocarcinoma; Bref=brefeldin A; CLL=chronic lymphocytic leukemia; CRC=colorectal carcinoma; CT=chemotherapy; FC=flow cytometry; GVHD=graft-versus-host disease; HCC=hepatocellular carcinoma; Iono=ionomycin; Mon=monensin; MPE=malignant pleural effusion; NA=not applicable or not mentioned in the article; NS=not significant; NSCLC=non-small cell lung carcinoma; PMA=phorbol 12-myristate 13-acetate; RT=radiotherapy; SCC=squamous cell carcinoma

Table 2. Correlations per measurement type

Target	Sample type	Measurement method	#analyses improved prognosis	#analyses poor prognosis	#analyses no effect	Total # analyses	Factor difference
IL-17	Serum	ELISA	1	5	4	10	0.2
	FFPE tissue	IHC	5	18	4	27	0.3
	Tumor associated fluid	ELISA	1	1	0	2	1.0
		Total	**7**	**24**	**8**	**39**	**0.3**
Th17	FFPE tissue	IHC Th17	1	0	1	2	NA
	Peripheral blood	Flow cytometry	4	2	3	9	2.0
	Tumor associated fluid	Flow cytometry	2	0	0	2	NA
		RT-PCR	1	0	0	1	NA
	Fresh frozen tissue	RT-PCR	0	0	2	2	NA
		Total	**8**	**2**	**6**	**16**	**4.0**

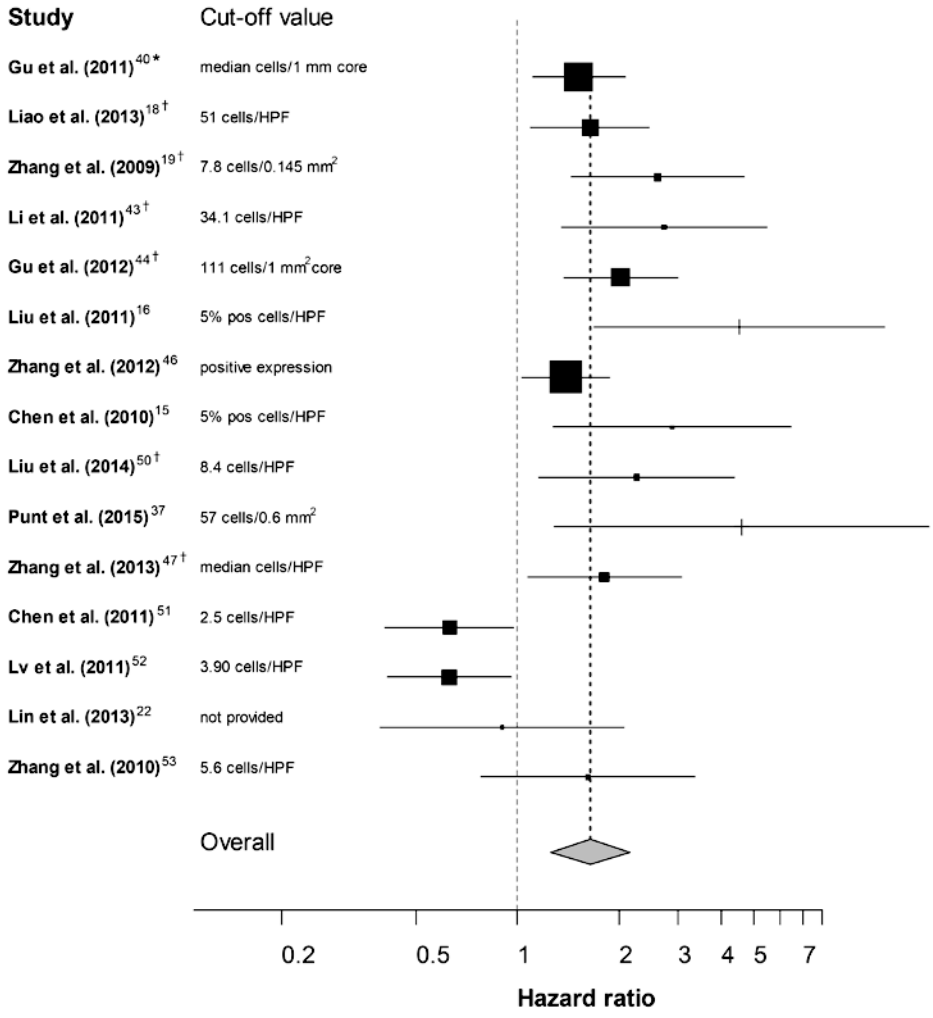
The number of analyses per sample and measurement type of IL-17 protein or Th17 cells showing a correlation with improved or poor prognosis or no effect is indicated. The final column denotes the ratio of the number of analyses showing a correlation with improved prognosis over the number of analyses showing a correlation with poor prognosis, as an indication of the factor difference. A white box indicates a correlation with improved survival, a dark grey box a correlation with poor survival and a light grey box no clear correlation.

A high number of IL-17$^+$ cells in tissue is correlated with poor survival

The total number of IL-17$^+$ cells was quantified on cancer tissue FFPE whole slides or tissue microarrays using immunohistochemistry. This type of analysis allows for quantification of the total number of IL-17$^+$ cells within the tumor microenvironment. IL-17 is expressed by different types of tumor infiltrating immune cells in cancer, predominantly neutrophils and mast cells.[37-39] The total number of IL-17$^+$ cells was correlated with poor prognosis in 18 out of 27 studies (Table 1.2).[15,16,18-20,30,37,40-50] Five studies reported on a correlation between a high number of IL-17$^+$ cells and improved survival.[21,28,29,51,52] It is important to note that in two of these five studies, the IL-17$^+$ cells were scored in areas with the densest lymphocytic infiltrate, one of which was on pancreatic ductal adenocarcinoma patients who had received immunotherapy (the correlation between IL-17 and survival was based on 12 patients).[21,29] Four studies did not observe a significant correlation between total IL-17$^+$ cells in the tumor and survival.[22,23,53,54] Again the scoring in two of these four studies had been performed in hot-spot or dense lymphocytic infiltrate areas, while only three of the 18 studies reporting on a negative correlation had focussed on hot-spots. Three more studies did

not focus on IL-17^{+} tumor infiltrating immune cells and are included with their reported correlations in Table 1 for completeness, but not in the quantitative analyses.[39,55,56] Collectively, 18 studies reported on a significant correlation between high IL-17 and poor prognosis, over 3.5 times more than the studies showing a correlation with improved prognosis (n=5, Table 2). To visualize the overall correlation, forests plots are shown for the hazard ratio of a high number of IL-17^{+} cells on overall (Figure 2A) and disease-free survival (Figure 2B). Of the 22 studies reporting on overall survival, 7 were excluded from the meta-analysis due to insufficient Cox regression data. Of the 16 studies reporting on disease-free survival, 4 were excluded due to insufficient Cox regression data.

A



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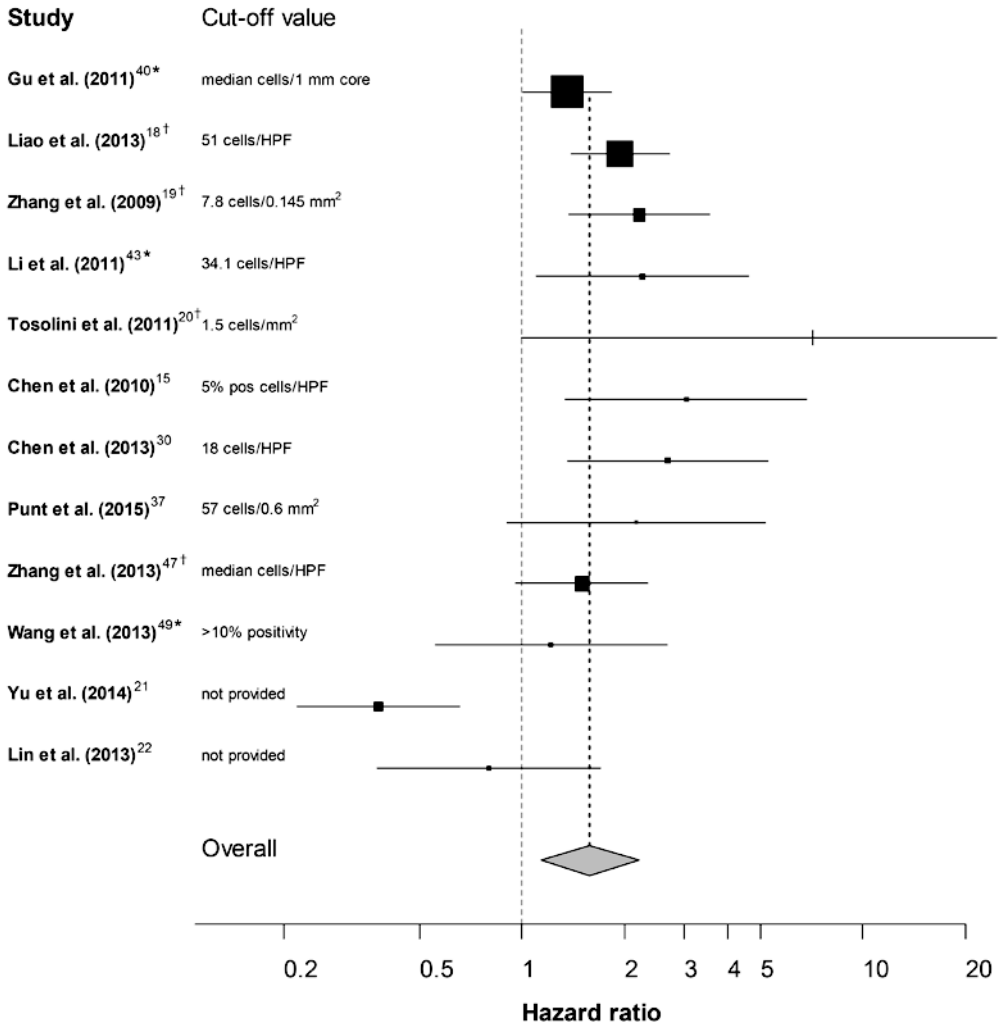

Figure 2. Forest plots for IL-17$^+$ cells in tissue

Schematic quantitative analyses of the studies on the number of IL-17$^+$ cells in FFPE tissue is shown by forest plots. Cox regression hazard ratios and 95% confidence intervals for the correlation between a high number of IL-17$^+$ cells and overall survival (A) and disease-free survival (B) were obtained from the articles or via personal communication with the authors. An asterisk (*) indicates that a multivariate Cox regression analysis was used because a univariate analysis was not provided. A dagger (†) indicates that part of the data were obtained via e-mail. The cut-off value used to divide the IL-17$^+$ cell frequency in a high and low group is indicated for comparison. The center of the random effects model represents the pooled hazard ratio, while the 95% confidence interval is represented by the diamond horizontal borders.

Correlation between IL-17 RNA expression in fresh frozen tissue and survival inconclusive

Two studies have analyzed IL-17 RNA expression in fresh frozen samples using RT-PCR (Table 1.3). Both studies, on small study populations, did not find associations with survival. One study analyzed IL-17 expression in tumor adjacent normal appearing biopsies (~10 cm from the tumor center) from 19 colorectal cancer patients.[57] The other study in 17 ovarian cancer patients only measured the presence of PCR products on agarose gel.[58] Insufficient data were available to conclude on an association between IL-17 RNA expression in fresh frozen tissue and survival.

A high number of Th17 cells in tissue is correlated with improved survival

The total number of Th17 cells can be quantified using a combination of a T cell marker and IL-17 in FFPE slides. Using immunohistochemistry, our group has shown that a high number of Th17 cells was correlated with improved prognosis in squamous cervical cancer,[37] while another study found a trend toward improved disease-free survival (p=0.06) in differentiated thyroid cancer (Table 1.3).[59] We did not include analyses on the ratio of the number of IL-17$^+$ cells over the number of CD3$^+$ or CD4$^+$ T cells, because we do not regard this as a measure for Th17 cells since IL-17 is also produced by other cell types.

A high number of Th17 cells in peripheral blood is correlated with improved survival

Flow cytometry was used to quantify the Th17 cell frequency among PBMCs, usually defined as CD4$^+$IL-17$^+$ cells (see Table 1.3 for details). A high number of Th17 cells was correlated with improved survival in four studies.[32,38,60,61] Two studies found a correlation with poor survival,[41,62] while three studies did not find a significant correlation.[33,63,64]

Two studies focused on a different aspect of the Th17 response and are included in the overview in Table 1 for completeness, but not in the quantitative analyses.[65,66] Notably, while two studies reported on a correlation between a high number of Th17 cells and poor prognosis, twice as many studies (n=4) reported on a correlation with improved prognosis (see Table 2).

A high number of Th17 cells in tumor associated fluids is correlated with improved survival

Tumor associated fluids have infrequently been studied for the correlation between IL-17 or Th17 numbers and survival (Table 1.4). Two studies have analyzed the number

of Th17 cells in lung cancer malignant pleural effusion by flow cytometry.[67,68] Both found a significant correlation between a high number of Th17 cells and improved overall survival.

One group has studied the correlation between high IL-17 protein levels in lung cancer malignant pleural effusion measured by ELISA and described a correlation with poor survival.[27] Another study found a correlation between high IL-17 protein levels in ovarian carcinoma ascites and improved survival.[69] Finally, a study in gastric cancer patients showed a significant correlation between high IL-17 RNA expression measured by qRT-PCR and improved survival in patients treated with curative resection.[70]

Collectively, of the five studies on tumor associated fluids, the studies quantifying Th17 cells using flow cytometry (n=2) and qRT-PCR (n=1) found a correlation with improved prognosis. Of the two studies quantifying IL-17 using ELISA, one found a correlation with improved, and one with poor prognosis.

Differences between cancer types

While functional differences between IL-17 and Th17 cells may be due to the cellular source of IL-17 and the accompanying immune response, this might also depend on the cancer type. In studies on liver cancer (n=13), a negative (n=9) or no significant (n=3) correlation was found between high IL-17 or Th17 cells and prognosis, except for the study of hepatocellular cancer treated with transarterial chemoembolization. All studies on colorectal cancer (n=6) also found a correlation between high IL-17 and poor prognosis (n=4) or no significant correlation (n=1), except for one study that reported on IL-17 being expressed mainly by tumor rather than tumor infiltrating immune cells. The studies on non-small cell lung cancer (n=3) reported a significant correlation between IL-17 and poor prognosis as well.

In contrast, all analyses described in six leukemia studies (n=8) showed a significant correlation between PBMC Th17 cells or serum IL-17 and improved prognosis (n=3) or no effect (n=4), except for one study of serum IL-17 in patients that received stem cell transplantation after myeloablative conditioning. This might indicate that the immune response in haematological malignancies may differ from solid tumors. Of the studies on ovarian cancer (n=4), two described a correlation between high IL-17 and improved survival. The other two groups did not find a significant correlation with disease-specific survival, but one of the studies described a correlation between high IL-17 and improved progression-free survival.

These findings indicate that there may be context specific effects on the IL-17 or Th17 cell immune response, although the number of studies per cancer type was too limited to determine whether the cancer type or sample type is more important for the effect on survival.

Discussion

The clinical impact of Th17 cells has remained unresolved in cancer.[71] The aim of this review was to identify the correlations between a high amount of IL-17 protein or high number of Th17 cells in human cancer and patient survival. Following an extensive electronic database search, publications were manually selected without format or language restrictions. Survival analyses were studied in the full article if any analysis regarding prognosis was mentioned in the abstract, minimizing the risk of publication bias. Although the risk of bias in included studies was limited, all studies used different cut-off levels to divide IL-17 or Th17 expression in a high and low expression group due to a lack of established cut-off levels. This study limitation makes it difficult to compare different studies directly.

The sample type studied proved to be crucial for the correlation with clinical outcome. This may partly be explained by a difference in cell source. Some tumor microenvironments may be more favorable for Th17 cells, while others may be more readily infiltrated by IL-17 producing neutrophils. Additionally, the method used determines whether Th17 cells, IL-17 protein or all IL-17 producing cells are measured. A high amount of IL-17 protein, predominantly produced by neutrophils and mast cells in cancer[37-39] and measured in serum, FFPE tissue and tumor associated fluids, was over three times more frequently correlated with poor than with improved prognosis. A meta-analysis could only be performed for IL-17 in FFPE tissue due to the limited number of studies on the other sample types. The forest plots clearly showed that a high number of $IL\text{-}17^+$ cells was correlated with an increased hazard ratio, despite the use of a range of cut-off values, which might depend on the type of cancer and analysis. In contrast, a high number of Th17 cells measured in FFPE tissue, peripheral blood or tumor associated fluids was four times more often correlated with improved than with poor prognosis. Since IL-17 RNA can generally not be quantified in neutrophils[37,72] the data obtained by RT-PCR analyses most likely represent IL-17 produced by Th17 cells. The PCR measurements in tumor associated fluids and fresh frozen tissue are thus regarded as an indicator of the Th17 cell frequency. Because of limited data available, we could not conclude on an association between IL-17 RNA expression and survival.

Th17 cells seemed to primarily have a tumor suppressing effect, whereas IL-17 was generally associated with poor outcome. IL-17 has been shown to be produced by only a small Th17 cell population.[37-39] The tumor promoting function can be explained by the role of IL-17 in inducing angiogenesis[73] and recruiting neutrophils.[74] Neutrophils have been reported to convert to a tumor promoting phenotype and to induce angiogenesis.[75] The immune cells capable of producing IL-17 include neutrophils as well as other cell types,[7-9] which may determine an important part of the clinical outcome. The tumor suppression by Th17 cells is probably due to different properties than the secretion of IL-17. Th17 cells might stimulate the Th1 and cytotoxic T cell tumor targeting immune responses.[76] Additionally, Th17 cells have been shown to have memory stem-cell like

properties and the ability to differentiate to Th1/Th17 cells that produce interferon-gamma.[77] Th17 cells may thus either directly or indirectly suppress tumorigenesis.

The type of IL-17 response is thus likely to be context dependent. Liver cancer, colorectal cancer and non-small cell lung cancer seem to be correlated with an unfavorable IL-17 response.[15,16,18-20,24-26,40-46] Leukemia on the other hand might provide an environment favorable for Th17 cells to suppress tumor growth.[32,38] Similarly, ovarian cancer might attract a tumor suppressing IL-17 response, as the majority of studies found a correlation with a favorable outcome.[28,69] A possible explanation might be that different microenvironments favor infiltration of or differentiation toward more or less tumor promoting immune cell phenotypes. Not only Th17 cells, but also innate cell types capable of producing IL-17 may be correlated with improved prognosis, as we and others have shown for mast cells.[37,39] Although we cannot discriminate whether the cancer type or method used is more important for the correlations found, it is likely that both are important for the cell source studied and thus clinical outcome.

Based on the findings described in the current review, cancer patients with high total IL-17 protein levels might benefit from anti-IL-17 treatment, blocking the tumor promoting response. Adoptive transfer of Th17 cells might be another promising treatment. The feasibility of both approaches needs to be investigated further. Human Th17 cells can be induced by a combination of IL-1β, IL-6 and IL-23, although the exact conditions required are still under debate.[78] The functions of differentially obtained Th17 cell populations should be determined by functional studies. Animal models may be helpful to clarify this, as the induction of Th17 cells by IL-6 and TGF-β is clearer in mice than in humans, although the described effects on survival are still contradictory.[12,79]

We conclude that while IL-17 primarily promotes tumorigenesis, the subpopulation of IL-17 producing Th17 cells seems to have a tumor suppressing effect. Future research should use methodology that makes a distinction between soluble IL-17 protein, Th17 cells and other IL-17$^+$ cells. This will help to determine whether IL-17 and Th17 cells should be targeted or used in a clinical setting.

Materials and Methods

Study design

A systematic search in the NCBI PubMed, Ovid Embase and Web of Science bibliographic databases was conducted without language restriction in collaboration with information specialist JML following the PRISMA guidelines.[80] Since IL-17 is frequently studied in autoimmune diseases and together with tumor necrosis factor, these terms were excluded as major topic. The full search terms are provided in Supplementary Table S9.

Selection criteria

All original research studies reporting on an IL-17A or Th17 cell measurement and overall (OS) or disease-free survival (DFS) in human cancer published until 10 September 2014 were included. Articles that did not meet all inclusion criteria (e.g. conference abstracts; studies on IL-17 producing γδTCR or $CD8^+$ cytotoxic T cells or only describing remission or progression-free survival) were excluded. All relevant references in reviews were manually checked for presence in the systematic search.

Data collection and analysis

Survival analyses, generally Kaplan-Meier survival curves, a log rank test and Cox regression analyses, but in some cases a Spearman's rank correlation,[33,68] Wilcoxon signed-rank test[29] or Satterwaithe t-test[61] were obtained. All included articles were reviewed by both SP and ESJ. If extracted data did not match, the data were discussed until a consensus was reached. Cox regression hazard ratios and confidence intervals were used to perform a meta-analysis. The authors of all articles that did not provide sufficient information on study details, clinico-pathological data or Cox regression analyses were contacted via e-mail. Due to the number of studies with sufficient data per sample type studied, only the analyses of the number of $IL\text{-}17^+$ cells in FFPE tissue were suitable for meta-analysis. To keep the data as comparable as possible, scores in the tumor center were used in the cases where data were reported on different scores (e.g. invasive margin, peritumor).

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Supplementary Table S1. Details of the studies on IL-17 in serum

Ref #	Inclusion criteria	Risk of bias (study level)	Risk of bias (outcome level)
25	absence of inflammatory disease, chronic liver disease, allergies or other concomitant diseases capable of interfering with the IL-17 assay		potential: cutoff value based on ROC curve
26	primary HCC without extrahepatic metastasis or prior therapy; Child-Pugh class A; no thrombus in main veins		potential: cutoff value based on ROC curve
31	not receiving multiple allogeneic SCTs	potential: consecutive patients, but relatedness of donor to patient and GVHD prophylaxis differed among patients	negligible: correlation determined for continuous variables
17	no prior RT/CT or other medical interventions		potential: cutoff value based on most significant difference in prognosis
24			potential: cutoff value based on ROC curve
32			
33		negligible: consecutive patients	negligible: measurement divided by median
34			negligible: measurements divided by median
36			negligible: correlation determined for continuous variables
35			

Inclusion criteria and risks of bias at study and outcome level provided for the studies on IL-17 measured by ELISA reported in Table 1. An empty cell means no data were reported on this topic. A shaded cell indicates a potential risk of bias. Abbreviations: CT=chemotherapy; GVHD=graft-versus-host disease; HCC=hepatocellular carcinoma; RT=radiotherapy

Supplementary Table S2. Details of the studies on IL-17 in tissue

Ref #	Inclusion criteria	Risk of bias (study level)	Risk of bias (outcome level)
40	no distant metastasis or receiving prior anticancer therapy	negligible: consecutive patients	negligible: measurements divided by median
18		negligible: consecutive patients	potential: cutoff value determined by minimum p value approach
41	no prior anticancer therapy, metastasis or concurrent autoimmune disease		
19	no prior anticancer therapy or concurrent autoimmune disease, HIV or syphilis		potential: cutoff value determined by minimum p value approach
42	no concurrent HCV/HIV infection, autoimmune disease or alcoholic liver disease		negligible: measurement divided by median
43			negligible: measurements divided by mean
44	no metastasis to lymph nodes beyond the hepatoduodenal ligament		negligible: measurements divided by median
20			potential: cutoff value determined by minimum p value approach
45			negligible: measurements divided by mean
16			potential: cutoff value arbitrarily chosen
46	no prior RT/CT treatment		negligible: measurement determined as positive/negative
15	no prior anticancer therapy		potential: cutoff value arbitrarily chosen
30	TNM stage I-III and available clinical follow-up data	potential: if no prechemotherapy biopsy was available, a post-chemotherapy sample was used to score IL-17	negligible: measurements divided by mean

50	effective resection, no prior anticancer therapy and without distant metastasis, autoimmune disease, HIV or syphilis		negligible: measurements divided by median
37	primary surgical treatment, no prior anticancer therapy and sufficient material available for analysis	negligible: consecutive patients	negligible: measurements divided by median
47	no concurrent autoimmune diseases or incomplete clinico-pathological data		negligible: measurements divided by median
49	no prior anti-cancer radio-, chemo-, and bio-therapy		negligible: measurement divided by more/less than 10% positive
48	no prior RT, CT or immune therapy or autoimmune or infectious diseases		negligible: measurements divided by median
51	no prior anticancer treatment or autoimmune disease		negligible: measurements divided by median
52	no autoimmune diseases, other esophageal cancers or prior anticancer treatment		negligible: measurements divided by median
21	FIGO stage II undergoing primary radical hysterectomy and pelvic lymphadenectomy without preoperative CT/RT		potential: cutoff value determined by minimum p value approach
28			potential: cutoff value determined by regression tree analysis
29	no liver metastases, grossly residual tumors, immediate recurrence, ampullary/neuro-endocrine/ undifferentiated cancer or autoimmune pancreatitis		potential: correlation determined for continuous variables, but extremely long surviving patients (n=6) were compared with poor surviving patients (n=6)
22			potential: cutoff value determined by minimum p value approach
53			negligible: measurements divided by median

23	stage III–IV with no prior anti-cancer or anti-inflammatory treatment and sufficient histological sections for immunohistochemical staining	potential: cutoff value determined by minimum p value approach
54		negligible: measurement divided by more/less than 25% positive
39*	no concurrent autoimmune diseases, distant metastasis or neoadjuvant therapy	negligible: measurements divided by median
55*	no prior CT/RT/anti-inflammatory treatment	negligible: measurement determined as positive/negative
56*	no prior anticancer therapy or patients that were immunocompromised	negligible: measurements divided by median

Inclusion criteria and risks of bias at study and outcome level provided for the studies on IL-17 measured by immunohistochemistry reported in Table 1. An empty cell means no data were reported on this topic. A shaded cell indicates a potential risk of bias. An asterisk behind a reference number indicates that the study was not included in the quantitative analyses. Abbreviations: CT=chemotherapy; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; RT=radiotherapy

Supplementary Table S3. Details of the studies on Th17 cells

Ref #	Inclusion criteria	Risk of bias (study level)	Risk of bias (outcome level)
37	primary surgical treatment, no prior anticancer therapy and sufficient material available for analysis	negligible: consecutive patients	negligible: measurements divided by median
59		negligible: consecutive patients	negligible: measurements divided in groups (absent, 1-10, > 10 pos cells/TMA spot)
41	no prior anticancer therapy, metastasis or concurrent autoimmune disease		
62	no prior RT/CT treatment		negligible: measurement divided by median
32			negligible: measurement divided by median

38		negligible: samples obtained before (n=55) and after treatment (n=11), effect remained significant	negligible: measurements divided by median
61	MART-1/Melan-A/HMB-45/tyrosinase/HLA-A*0201 expression; no autoimmune disease, steroid dependence or prior ipilimumab treatment		negligible: measurements divided by median
60	patients aged 18 - 75 years with the largest tumor diameter ≥ 5 cm, no previous treatment or concurrent diseases (see reference for details)	negligible: consecutive patients	negligible: measurements divided by median
33		negligible: consecutive patients	negligible: measurement divided by median
64			negligible: means compared
63			negligible: measurements divided by integer value near the mean/median value
65*	unresectable distant metastases at the time of blood draw, T cell reactivity against Melan-A and available survival follow-up data		negligible: measurement determined as positive/negative
66*			negligible: measurements divided by median
57			
58		potential: sample size possibly too small	potential: not very sensitive method (presence of RT-PCR product bands)

Inclusion criteria and risks of bias at study and outcome level provided for the studies on Th17 cells measured by immunohistochemistry, flow cytometry or PCR analysis reported in Table 1. An empty cell means no data were reported on this topic. A shaded cell indicates a potential risk of bias. An asterisk behind a reference number indicates that the study was not included in the quantitative analyses. Abbreviations: CT=chemotherapy; RT=radiotherapy

Supplementary Table S4. Details of studies on IL-17 or Th17 cells in tumor associated fluid

Ref #	Inclusion criteria	Risk of bias (study level)	Risk of bias (outcome level)
27		negligible: consecutive patients	potential: cutoff value based on ROC curve
69		potential: 2 different chemotherapy regimens were given	negligible: measurements divided by median
67	no anticancer therapy, corticosteroids, nonsteroid anti-inflammatory drugs, invasive procedures in the pleural cavity or suffering chest trauma within 3 months prior to hospitalization		negligible: measurements divided by median
68	not receiving disease-modifying therapy; no autoimmune disease, empyema, chest trauma, pregnancy or lactation before recruitment		negligible: correlation determined for continuous variables
70	not receiving prior anticancer therapy or having autoimmune disease, inflammatory bowel disease or viral infections		negligible: measurement divided by median

Inclusion criteria and risks of bias at study and outcome level provided for the studies on IL-17 and Th17 measured on tumor associated fluids reported in Table 1. An empty cell means no data were reported on this topic. A shaded cell indicates a potential risk of bias.

Supplementary Table S5. Clinico-pathological data of the studies on IL-17 in serum

Ref #	Cancer type	Histology	Stage	Female (%)	Median age (range)	Median follow-up (months) (range)
25	NSCLC	46,9% SCC, 53,1% AC		40%	54 (mean 59 ± 11)	24 (3 - 81) for living patients
26	HBV-related HCC	71% Edmondson-Steiner grade I-II, 30% III-IV	4% BCLC 0, 79% A, 17% B	13%	53 (46 - 60)	20
31†	Leukemia treated with allogeneic SCT after myeloablative conditioning	55% AML, 40% ALL, 5% CML	87% standard, 13% advanced	42%	32 (15 – 57)	17 (9 - 26) for surviving transplants
17	Gastric carcinoma	52% differentiated, 48% undifferentiated	69% TNM I-II, 31% stage III-IV			
24†	CRC	4% well, 89% moderate, 6% poorly differentiated	18% TNM I, 37% II, 28% III, 17% IV	45%	67 (30 - 91)	mean 44 (32-60)
32	Acute leukemia	68% AML, 32% ALL		45%	19 - 63	
33	CLL		31% Rai 0, 21% I, 30% II, 6% III, 12% IV	55%	64 (38 - 87)	9 (1 - 124)
34	CLL		64% Rai 0-1, 25% 2-4		65 (34 - 91)	
36†	Pancreatic AC		11% TNM II, 24% III, 65% IV	37%	65 (31 - 80)	7 (1 - 66)
35	Multiple myeloma		12% ISS I, 36% II, 52% III	38%	mean 60 ± 7	23 (8 - 35)

Tumor histology and stage, female/male distribution and median age and follow-up are provided for the studies on IL-17 measured by ELISA reported in Table 1. Most studies provided the median and range of the age and follow-up distributions. Indications are given in cases where other units were provided, mainly the mean and standard deviation. Data of the studies by Tseng et al.[24], Yamada et al.[17] and Hus et al.[33] are provided for the total study cohort rather than the subpopulation IL-17 was measured in. An empty cell means no data were reported on this topic. A dagger behind a reference number indicates that data have (partially) been obtained via e-mail. Abbreviations: AC=adenocarcinoma; ALL=acute lymphoid leukemia; AML=acute myeloid leukemia; BCLC=Barcelona Clinic Liver Cancer Classification; CLL=chronic lymphocytic leukemia; CML=chronic myeloid leukemia; CRC=colorectal carcinoma; HCC=hepatocellular carcinoma; ISS=International Staging System; NSCLC=non-small cell lung carcinoma; SCC=squamous cell carcinoma

Supplementary Table S6. Clinico-pathological data of the studies on IL-17 in tissue

Ref #	Cancer type	Histology	Stage	Female (%)	Median age (range)	Median follow-up (months) (range)
40	HCC	79% Edmonson grade I-II, 21% III-IV	48% TNM I, 52% II-III	14%	51% ≤ 50	60 (2 - 74)
18†	HCC	73% grade I-II, 27% III-IV	67% TNM I, 33% II-III	16%	52% ≤ 53	53 (18-79)
41	HCC					
19†	HCC	56% Edmonson grade I-II, 44% III-IV	76% TNM I-II, 24% III	12%	46 (17 - 71)	44 (2-80)
42	HCC	16% well, 70% moderate, 14% poorly differentiated	61% TNM I-II, 39% III-IV	11%	mean 54 ± 10	36 (2 - 73)
43	HCC		58% TNM I-II, 42% III-IV	15%	80% ≤ 60	
44†	Intrahep. cholangio-carcinoma	massforming type; 70% Edmonson grade I-II, 30% III-IV	51% TNM I, 23% II, 26% III	50%	55 (18 - 78)	13 (4 – 111)
20†	CRC	22% mucinous colloid type; 63% well, 35% moderate, 2% poorly differentiated	12% TNM I, 33% II, 29% III, 26% IV	84%	26% < 65	36 (29-55)
45	CRC	15% well, 56% moderate, 30% poorly differentiated	33% TNM I-II, 67% III-IV	44%		
16	Colorectal AC	83% tubular, 17% mucinous type; 65% well-moderate, 35% poorly differentiated	TNM III	40%	62% < 60	
46	NSCLC	43% SCC, 52% AC, 5% ASC	41% TNM I, 26% II, 32% III	35%	mean 65 (40 - 73)	30
15	NSCLC	31% AC, 44% SCC, 25% other; 19% well-moderate, 81% poorly differentiated	63% TNM I-II, 37% III	21%	52 (29 - 77)	
30	Breast carcinoma	82% ductal, 4% lobular, 4% mixed, 10% mucinous, 1% metaplastic; 30% grade I, 40% II, 30% III	20% TNM I, 46% II, 34% III	100%	51 (23 - 78)	mean 67 (7 - 144)

50†	Gastric carcinoma	24% well-moderate, 75% poorly differentiated	44% TNM is/I/II, 56% III	30%	60 (33 - 89)	51 (39 - 57)
37	Cervical carcinoma	100% SCC	77% FIGO IB, 22% IIA, 1% IIB; 69% TNM I, 28% II, 3% III, 1% IV	100%	45 (22 - 87)	100 (1 - 296)
47†	Gall-bladder carcinoma	29% well, 38% moderate, 33% poorly differentiated	7% TNM I, 36% II, 46% III, 12% IV	61%	mean 66 ± 12	mean 39 (2 - 76)
49	Laryngeal carcinoma	100% SCC	24% TNM I, 23% II, 25% III, 28% IV	3%	59	58 (38-85)
48	Pancreatic AC	26% well, 33% moderate, 41% poorly differentiated	15% TNM I, 33% II, 39% III, 13% IV	35%	mean 61 (43 - 75)	5 - 48
51	Gastric AC	3% well, 21% moderate, 76% poorly differentiated	4% TNM I, 37% II, 49% III, 10% IV	33%	58 (17 - 85)	61 (0 - 82)
52	Esophag. carcinoma	100% SCC	65% TNM I-II, 35% III-IV	22%	56 (33 - 79)	44 (1 - 87)
21	Cervical carcinoma	86% SC, 12% AC, 2% ASC	57% FIGO IIA1, 41% IIA2, 2% IIB	100%	17% < 40	
28	Ovarian carcinoma with recurrence	94% high-grade serous papillary carcinoma	6% FIGO II, 84% III, 4% IV	100%	34 - 77	
29	Pancreatic ductal AC					
22	HCC	48% grade I-II, 52% III-IV	62% TNM I-II, 38% III	8%	51 (20 - 71)	
53	Nasopha-ryngeal carcinoma	1% SCC, 12% NKC, 87% UC	6% TNM I, 30% II, 37% III, 27% IV	21%	49 (22 - 73)	
23	Epithelial ovarian cancer	74% serous, 6% mucinous, 10% endometrioid, 1% clear cell, 10% AC; 12% grade I, 89% II-III	90% FIGO III, 10% IV	100%	53 (27 - 81)	
54	Giant cell tumors of bone	54% Campanacci grade I-II, 46% III	61% Enneking T1, 39% T2	55%	22% > 30	

39*	Esophageal SCC	19% well, 57% moderate, 24% poorly differentiated	7% TNM I, 46% IIA, 2% IIB, 34% III, 2% IV	26%	56 (23 - 82)	29 (2 - 157)
55*†	CRC	42% well, 29% moderate, 10% poorly differentiated	5% Duke's stage A, 32% B, 33% C, 29% D	41%	41% < 60	
56*	Glio-blastoma		TNM IV	56%	47 (14 - 65)	13 (4 - 24)

Tumor histology and stage, female/male distribution and median age and follow-up are provided for the studies on IL-17 measured by immunohistochemistry reported in Table 1. Most studies provided the median and range of the age and follow-up distributions. Indications are given in cases where other units were provided, mainly the mean and standard deviation. Data of the study by Lin et al.[22] are provided for the total study cohort rather than the subpopulation IL-17 was measured in. An empty cell means no data were reported on this topic. An asterisk behind a reference number indicates that the study was not included in the quantitative analyses. A dagger behind a reference number indicates that data have (partially) been obtained via e-mail. Abbreviations: AC=adenocarcinoma; CRC=colorectal carcinoma; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HCC=hepatocellular carcinoma; NSCLC=non-small cell lung carcinoma; SCC=squamous cell carcinoma

Supplementary Table S7. Clinico-pathological data of the studies on Th17 cells

Ref #	**Cancer type**	**Histology**	**Stage**	**Female** (%)	**Median age** (range)	**Median follow-up** (months) (range)
37	Cervical carcinoma	100% SCC	67% FIGO IB, 31% IIA; 63% TNM I, 33% II, 2% III, 2% IV	100%	40 (22 - 75)	85 (2 - 296)
59	Differentiated thyroid carcinoma	95% papillary, 5% follicular	59% TNM I, 11% II, 15% III, 15% IV	82%	54% < 45	
41	HCC					
62	Gastric carcinoma	25% moderate, 75% poorly differentiated	28% TNM I-II, 72% III-IV	34%	54 (31 - 69)	
32	Acute leukemia	68% AML, 32% ALL		45%	19 - 63	
38	CLL		30% Rai 0, 35% I, 15% II, 12% III, 8% IV			

61†	Melanoma treated with ipilimumab (a-CTLA4)		39% TNM IIIc, 61% IV	41%	49% < 56	26 (14-68)
60†	HCC treated with transarterial chemoem-bolization		TNM III	20%	55 (26 - 71)	11 (1 - 35)
33	CLL		31% Rai 0, 21% I, 30% II, 6% III, 12% IV	55%	64 (38 - 87)	9 (1 - 124)
64†	hematologic malignancy treated with allogeneic HSCT	13% MDS, 63% AML, 23% ALL		23%	30 (2-66)	7
63†	HCC		BCLC A or B	31%	62 (41-81)	14
65*†	Melanoma		TNM IV	33%	53 (19 - 90)	12 (1-135)
66*†	Acute myeloid leukemia	7% M1, 15% M2, 27% M3, 30% M4, 18% M5, 2% M6, 1% M7		44%	46 (16 - 79)	9
57	CRC					
58	Ovarian carcinoma	24% serous cyst AC, 6% mucinous cyst AC, 41% clear cell, 29% endometr. AC	41% FIGO I, 12% II, 35% III, 12% IV			

Tumor histology and stage, female/male distribution and median age and follow-up are provided for the studies on Th17 measured by immunohistochemistry, flow cytometry or PCR analysis reported in Table 1. Most studies provided the median and range of the age and follow-up distributions. Indications are given in cases where other units were provided, mainly the mean and standard deviation. Data of the studies of Sarnaik et al.[61] and Hus et al.[33] are provided for the total study cohort rather than the subpopulation Th17 cells were measured in. An empty cell means no data were reported on this topic. An asterisk behind a reference number indicates that the study was not included in the quantitative analyses. A dagger behind a reference number indicates that data have (partially) been obtained via e-mail. Abbreviations: AC=adenocarcinoma; ALL=acute lymphoid leukemia; AML=acute myeloid leukemia; BCLC=Barcelona Clinic Liver Cancer Classification; CLL=chronic lymphocytic leukemia; CRC=colorectal carcinoma; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HCC=hepatocellular carcinoma; SCC=squamous cell carcinoma

Supplementary Table S8. Clinico-pathological data of the studies on IL-17 or Th17 cells in tumor associated fluid

Ref #	Cancer type	Histology	Stage	Female (%)	Median age (range)	Median follow-up (months) (range)
27	Lung cancer with MPE	86% AC, 6% SCC, 8% small cell ca		54%	mean 56 ± 13	
69	Ovarian carcinoma	64% serous/ mucinous/endometroid, 36% clear cell/ undifferentiated; 13% grade G1,15% G2,69% G3,2% G4	6% FIGO II, 61% III, 33% IV		mean 61 (25 - 80)	
67	Lung carcinoma with MPE	37% SCC, 63% AC		60%	64 (32 - 81)	
68	Lung AC with pleura metastasis			33%	mean 50 ± 9	
70	Gastric carcinoma	52% differentiated, 48% undifferentiated	51% TNM I, 23% II, 27% III	27%	44% ≤65	61 (1 - 99)

Tumor histology and stage, female/male distribution and median age and follow-up are provided for the studies on IL-17 and Th17 measured in tumor associated fluids reported in Table 1. Most studies provided the median and range of the age and follow-up distributions. Indications are given in cases where other units were provided, mainly the mean and standard deviation. An empty cell means no data were reported on this topic. Abbreviations: AC=adenocarcinoma; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; MPE=malignant pleural effusion; SCC=squamous cell carcinoma

Supplementary Table S9. Database search strategies

Database	Search Strategy
PubMed	(("Interleukin-17"[majr] OR "Interleukin-17"[tiab] OR "Interleukin 17"[tiab] OR "Interleukin17"[tiab] OR "IL17"[tiab] OR "IL-17"[tiab] OR "Th17 Cells"[Majr] OR "Th17"[tiab] OR "Th-17"[tiab]) AND ("Neoplasms"[majr] OR "Neoplasms"[tiab] OR "Neoplasm"[tiab] OR "cancer"[tiab] OR "carcinoma"[tiab] OR "malignancy"[tiab] OR "malignancies"[tiab] OR "tumor"[tiab] OR "tumour"[tiab] OR "tumors"[tiab] OR "tumours"[tiab])) NOT ("Tumor Necrosis Factors"[Majr] OR "Tumor necrosis factor"[ti] OR "Tumour necrosis factor"[ti] OR "Tumor necrosis factors"[ti] OR "Tumour necrosis factors"[ti] OR "TNF"[ti] OR "Autoimmune Diseases"[Majr] OR “autoimmune”[ti] OR “auto-immune”[ti] OR “autoimmunity”[ti] OR “arthritis”[majr] OR “arthritis”[ti] OR “arthritic”[ti] OR “multiple sclerosis”[ti] OR “psoriasis”[majr] OR “psoriasis”[ti] OR “inflammatory bowel diseases”[majr] OR “inflammatory bowel disease”[ti] OR “inflammatory bowel diseases”[ti] OR “Crohn Disease”[majr] OR “crohn”[ti] OR “crohn’s”[ti] OR “lupus”[ti] OR “colitis”[majr] OR “colitis”[ti])
Embase	((*interleukin 17/ OR "Interleukin-17".ti,ab. OR "Interleukin 17".ti,ab. OR "Interleukin17".ti,ab. OR "IL17".ti,ab. OR "IL-17".ti,ab.) AND (*neoplasm/ OR "Neoplasms".ti,ab. OR "Neoplasm".ti,ab. OR "cancer".ti,ab. OR "carcinoma".ti,ab. OR "malignancy".ti,ab. OR "malignancies".ti,ab. OR "tumor".ti,ab. OR "tumour".ti,ab. OR "tumors".ti,ab. OR "tumours".ti,ab.)) NOT (*tumor necrosis factor/ OR "Tumor necrosis factor".ti. OR "Tumour necrosis factor".ti. OR "TNF".ti. OR exp *autoimmune disease/ OR "autoimmune".ti. OR "auto-immune".ti. OR "autoimmunity".ti. OR exp *arthritis/ OR "arthritis".ti. OR "arthritic".ti. OR *multiple sclerosis/ OR "multiple sclerosis".ti. OR exp *psoriasis/ OR "psoriasis".ti. OR *inflammatory bowel disease/ OR "inflammatory bowel disease".ti. OR "inflammatory bowel diseases".ti. OR *crohn disease/ OR *ulcerative colitis/ OR "crohn".ti. OR "crohn’s".ti. OR "lupus".ti. OR "colitis".ti.)
Web of Science	(TS=("Interleukin-17" OR "Interleukin 17" OR "Interleukin17" OR "IL17" OR "IL-17") AND TS=("Neoplasms" OR "Neoplasm" OR "cancer" OR "carcinoma" OR "malignancy" OR "malignancies" OR "tumor" OR "tumour" OR "tumors" OR "tumours")) NOT TI= ("tumor necrosis factor*" OR "tumour necrosis factor*" OR "TNF" OR "autoimmune" OR "auto-immune" OR "autoimmunity" OR "arthritis" OR "arthritic" OR "multiple sclerosis" OR "psoriasis" OR "inflammatory bowel disease" OR "inflammatory bowel diseases" OR "crohn" OR "crohn’s" OR "lupus" OR "colitis")

The specific search strategies per database are indicated.