cancers

MDPI

Article

Combined Systematic Review and Transcriptomic Analyses of Mammalian Aquaporin Classes 1 to 10 as Biomarkers and Prognostic Indicators in Diverse Cancers

Pak Hin Chow, Joanne Bowen and Andrea J Yool *

Adelaide Medical School, University of Adelaide, Adelaide SA 5005, Australia; pakhin.chow@adelaide.edu.au (P.H.C.); joanne.bowen@adelaide.edu.au (J.B.)
* Correspondence: andrea.yool@adelaide.edu.au; Tel.: +61-8-8313-3359

Received: 1 June 2020; Accepted: 7 July 2020; Published: 15 July 2020

Abstract: Aquaporin (AQP) channels enable regulated transport of water and solutes essential for fluid homeostasis, but they are gaining attention as targets for anticancer therapies. Patterns of AQP expression and survival rates for patients were evaluated by systematic review (PubMed and Embase) and transcriptomic analyses of RNAseq data (Human Protein Atlas database). Meta-analyses confirmed predominantly negative associations between AQP protein and RNA expression levels and patient survival times, most notably for AQP1 in lung, breast and prostate cancers; AQP3 in esophageal, liver and breast cancers; and AQP9 in liver cancer. Patterns of AQP expression were clustered for groups of cancers and associated with risk of death. A quantitative transcriptomic analysis of AQP1-10 in human cancer biopsies similarly showed that increased transcript levels of AQPs 1, 3, 5 and 9 were most frequently associated with poor survival. Unexpectedly, increased AQP7 and AQP8 levels were associated with better survival times in glioma, ovarian and endometrial cancers, and increased AQP11 with better survival in colorectal and breast cancers. Although molecular mechanisms of aquaporins in pathology or protection remain to be fully defined, results here support the hypothesis that overexpression of selected classes of AQPs differentially augments cancer progression. Beyond fluid homeostasis, potential roles for AQPs in cancers (suggested from an expanding appreciation of their functions in normal tissues) include cell motility, membrane process extension, transport of signaling molecules, control of proliferation and apoptosis, increased mechanical compliance, and gas exchange. AQP expression also has been linked to differences in sensitivity to chemotherapy treatments, suggesting possible roles as biomarkers for personalized treatments. Development of AQP pharmacological modulators, administered in cancer-specific combinations, might inspire new interventions for controlling malignant carcinomas.

Keywords: water channel; AQP; metastasis; transcriptomics; forest plot; prognosis; patient survival

1. Introduction

Membrane channels and transporters are essential for the balanced control of ion and fluid homeostasis and electrical signaling [1] and serve key roles in cell proliferation, migration, apoptosis and differentiation, which are increasingly being recognized as relevant for cancer progression [2]. Aquaporins are known as channels that facilitate passive water transport in response to osmotic gradients created by active transport and net displacement of solutes across cell membranes or tissue barriers [3]. Several classes of mammalian aquaporin (AQP) channels have been linked to cancer progression via effects on angiogenesis, proliferation and metastasis [4]. AQPs have been proposed as part of the volume regulatory engine driving process extension during motility [5–8]. Inhibitors of

AQPs are of interest as potential tools for impairing the protrusion and displacement steps in metastatic cell movement [8]. Pharmacological modulators of aquaporin channels derived from loop diuretics, metal-containing organic compounds, plant natural products and other small molecules are opening opportunities to explore the therapeutic potential of AQPs as novel targets [8].

AQP overexpression has been reported in at least 12 different tumor cell types [9]. Interestingly, different classes of AQPs are upregulated for different cancer types, in which tumor-promoting effects are not reproduced by substitution of other AQP classes [10]. Positive associations between histological tumor grades and levels of AQP expression often involve AQP subtypes in the pathology that are not expressed in normal tissues at the site of origin [11]. This reliance on an AQP subtype indicates that the tumorigenic roles are unlikely to stem simply from increasing water channel activity and osmotic water flux, but must be exploiting features such as substrate permeability, mechanisms of regulation, subcellular localization or other properties that differ between subtypes. AQPs have been proposed to promote cancer metastasis by facilitating tumor cell migration [6,7,12], but a broader range of possible functions is likely, given the expanding understanding of their diverse roles in normal cell physiology.

Thirteen classes (AQP0–AQP12) have been identified in higher mammals [13,14], expressed in kidneys, lung airways, eyes, brain, glands, vascular system and other tissues [15,16]. Classical aquaporins (AQPs 0, 1, 2, 4, 5, 6 and 8) were initially viewed as water-selective channels, but further evidence has established capacity for transport of gases, urea, hydrogen peroxide, ammonia and, in some cases, charged particles [17,18]. Aquaglyceroporins (AQPs 3, 7, 9 and 10) are permeable to glycerol as well as water. AQPs 11 and 12 are more distantly related to other mammalian AQPs, based on amino acid sequence; functions and regulation remain to be fully defined [19]. Diverse contributions of AQP classes could augment pro-cancer conditions by enhancing signaling via nitric oxides or hydrogen peroxide [20–23], facilitating gas exchange of O_2 and CO_2 [24,25], promoting cell cycle progression [26], providing metabolic support [27,28], mediating dual ion and water fluxes for localized control of process extension [12], driving angiogenesis [29], boosting mechanical compliance needed for rapid volume changes [6,30] and other processes. Dynamic translocation between membrane and intracellular vesicle pools is controlled by signaling; for example, AQP2 localization depends on cyclic AMP-dependent kinase activity [31], and AQPs are associated via protein–protein interactions into signaling complexes [32–34]. Apoptotic responses associated with AQPs 4, 8 and 9 could involve water and monovalent ion loss, causing the hallmark cell shrinkage which precedes programmed cell death [35–37], suggesting AQPs in some cases might also have anticancer effects depending on the balance of outcomes.

Strong evidence for AQPs in cancer cell migration and metastasis comes from in vitro pharmacological studies, as well as in vivo mouse models [7,8,38]. In the process of metastasis, cancer cells escape normal control mechanisms, invade surrounding tissues and spread to other parts of the body, accounting for the second greatest cause of mortality globally, as ranked by the World Health Organization, based on 9.6 million deaths in 2018 [39]. As the average human lifespan lengthens, the incidence of cancer in the aging population is increasing, with numbers expected to rise by 70% in the next two decades [40]. Treatment options, including surgery, chemotherapy and radiotherapy, are aimed primarily at inhibiting cancer proliferation [41], now recognized as being mediated in part by activation of the immune system, and driving new interest in combined immunotherapies [42]. However, the recurrence of cancers at new sites indicates that additional treatments targeting cancer metastasis are greatly needed [43].

The hypothesis tested in this work was that levels of expression of different classes of AQPs (based on data for transcript levels, protein levels or both) show distinctive patterns that are associated with the risk of death in people with cancers. The combined analyses here are the first, to our knowledge, to systematically review all classes of aquaporins in diverse cancer types and to correlate findings with transcriptomic data from human cancer biopsies.

2. Results

A total of 1546 papers were identified from the first level of screening of PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Embase (https://www.embase.com/) databases by using the search keywords (Table 1). After excluding duplicate search results, 361 records were selected for second-level screening of titles and abstracts. After careful assessment, 285 records were retrieved for full review. Papers lacking sufficient focus on AQPs were excluded (with reasons logged), leaving a final set of 224 papers included in this review (Figure 1). Within this final set, the largest proportion of studies addressed AQP1, followed by AQP5, AQP4, AQP3 and AQP9, for a diverse array of cancer types, including brain, lung, breast and colorectal cancers.

Table 1. Search terms used for data collection. (Searches combined the left and right sets with AND).

Embase	
Neoplasm/exp OR cancer *: tiab OR neoplasm *: tiab OR Metastas *: tiab OR Tumor *: tiab OR Tumor *: tiab	Aquaporin/de OR "Aquaporin1"/de OR "Aquaporin2"/de OR "Aquaporin3"/de OR "Aquaporin4"/de OR "Aquaporin5"/de OR "Aquaporin6"/de OR "Aquaporin7"/de OR "Aquaporin8"/de OR "Aquaporin9"/de OR "Aquaporin10"/de OR "Aquaporin11"/de OR "Aquaporin12"/de OR "Aquaporin0"/de OR Aquaporin *: tiab OR "Water channel *": tiab OR AQP *: tiab OR CHIP28 *: tiab
PubMed	
Neoplasms[mh] OR cancer *[tiab] OR neoplasm *[tiab] OR "Neoplasm Metastasis" [mh] OR Metastas *[tiab] OR Tumor *[tiab] OR Tumor *[tiab]	Aquaporins[mh] OR Aquaporin *[tiab] OR "Water channel *"[tiab] OR AQP *[tiab] OR CHIP28 *[tiab] OR MIP *[tiab]

* The asterisk is a wildcard symbol used to broaden search terms for literature database queries.

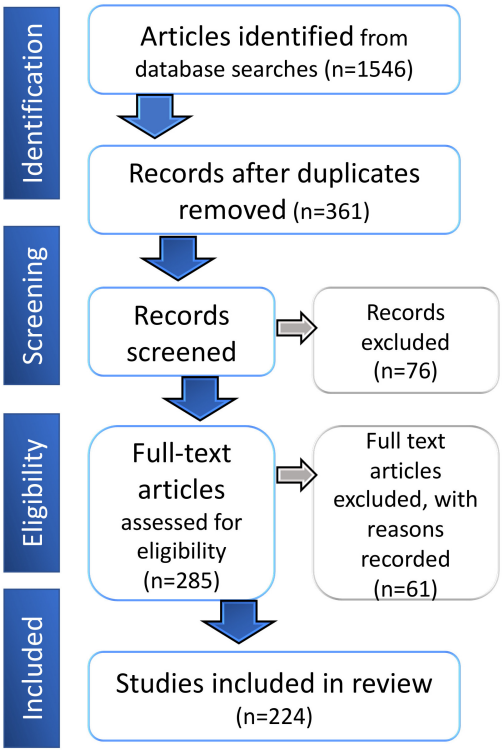

Figure 1. Flow diagram showing the process of the literature evaluation for the systematic review.

Forest plots (Figure 2) summarizing the survival probabilities of people with cancers reported in the published literature were correlated with levels of expression of different classes of AQPs (based on RNA, protein levels or both), as determined from compiled data from all papers in the final set, which included survival analyses (n = 30). Results indicated strongly negative correlations. AQP1 appeared to be associated with higher risks of death in lung adenocarcinoma patients with a four-fold increase in hazard ratio (HR 4.0) and in pleural mesothelioma (HR 2.7), as well as breast, prostate and some colon cancers (HRs 2.6 to 3.4). Dramatic increases in patient risk were observed for AQP3 in esophageal cancer (HR18.4), and AQP9 in liver cancer (HR 10.8). High hazard ratios for gastric cancer patients correlated with increased AQPs 2, 8 and 10 expression, contrasting with a reduced hazard ratio seen when AQP3 or AQP9 levels were increased. For breast cancer patients, higher hazard ratios were observed with increased AQPs 1 and 3 expression; possible associations with other AQP classes remain to be evaluated. These data support the idea that AQPs are upregulated in cancers and that the specific classes of AQPs involved and patterns of co-regulation depend on the cancer subtype [10]. It is important to note that, in some cases, such as hepatocellular carcinoma, increased expression of AQP1 is associated with the vasculature, and rarely the cancer cells themselves [44].

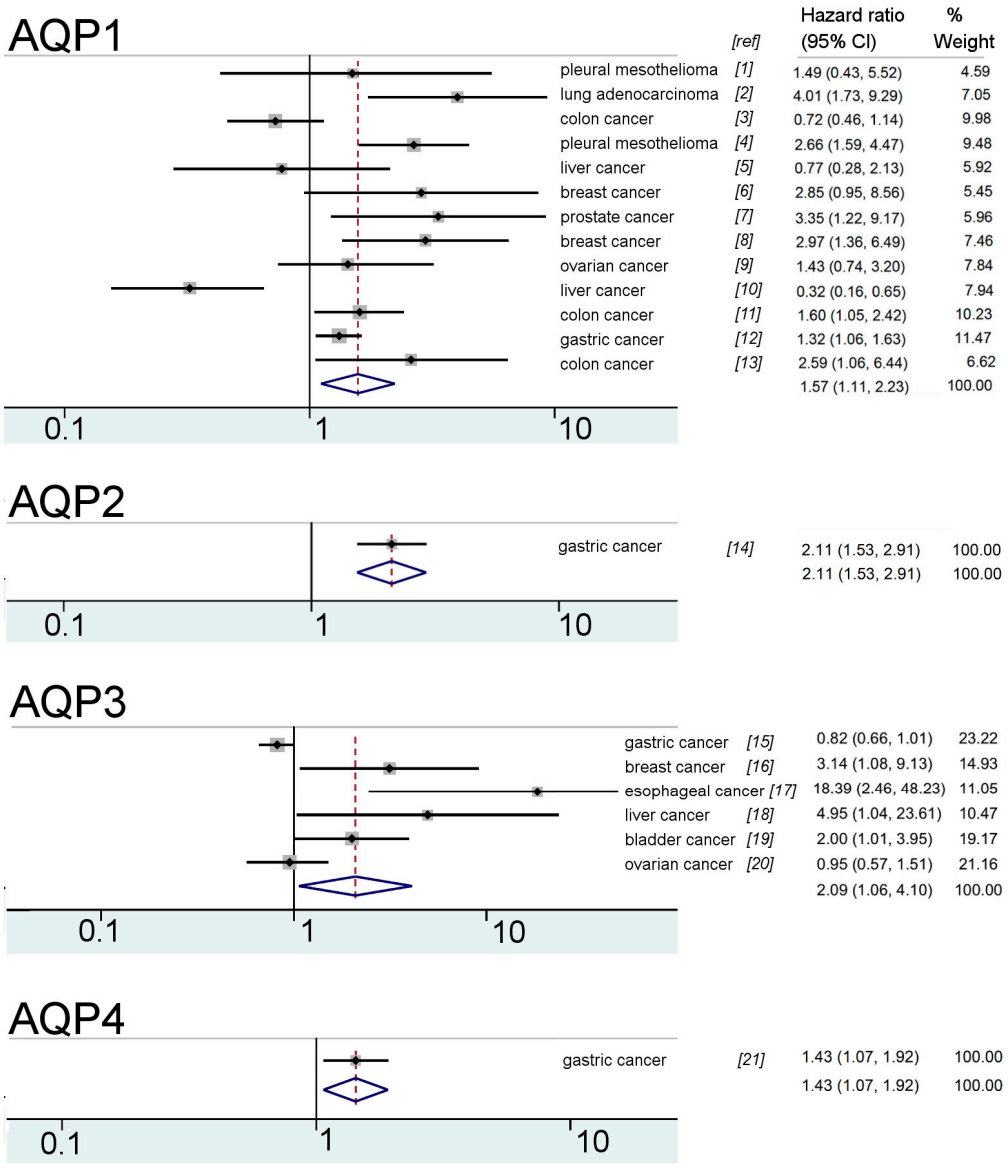

Figure 2. *Cont.*

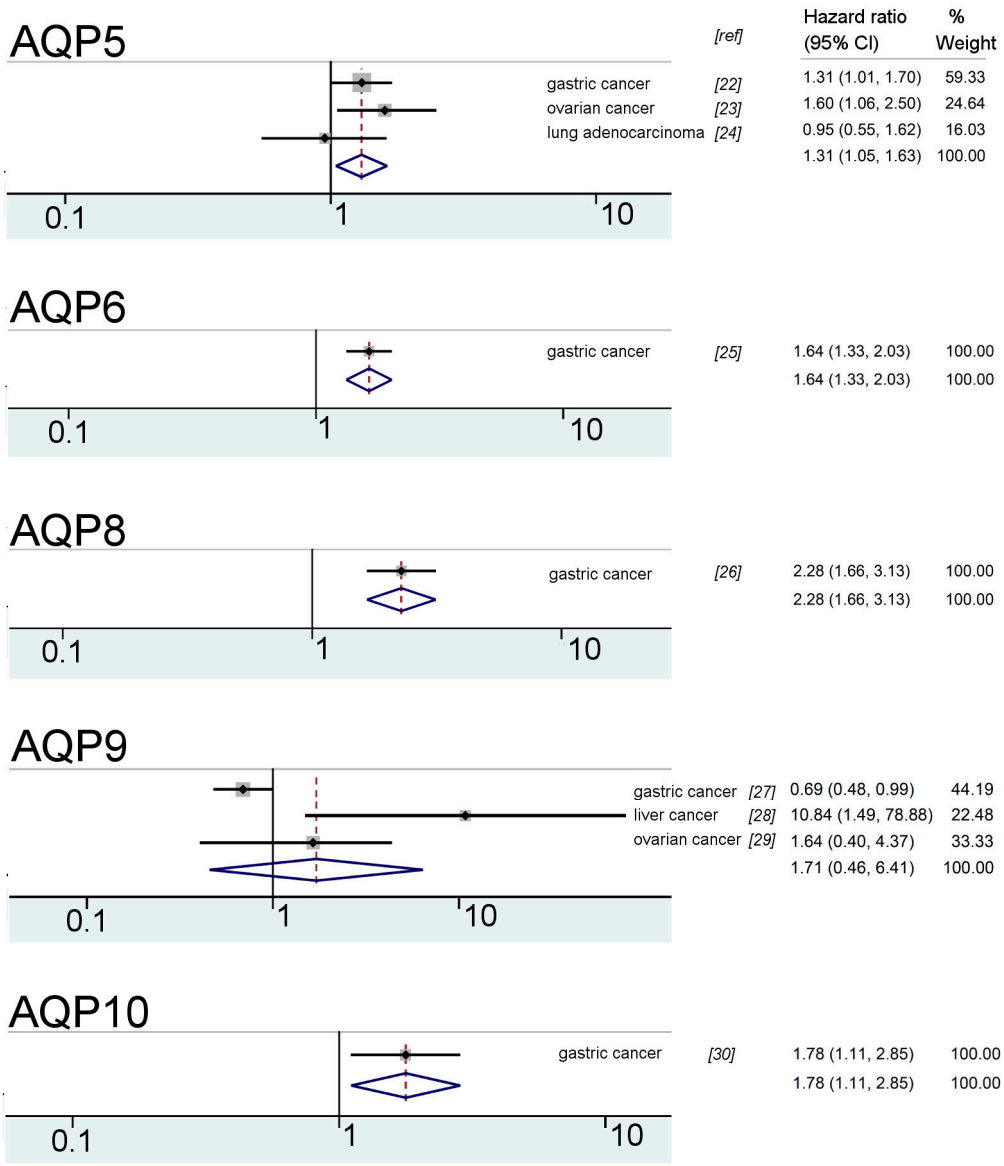

Figure 2. Forest plots compiled for aquaporin (AQP) classes, with hazard ratio and confidence interval (CI) data extracted from the published literature, based on analyses of levels of protein, RNA or both. References listed in the figure as [ref] for data sources are as follows: *[1]* Angelico, 2018 [45]; *[2,24]* Bellezza, 2017 [46]; *[3]* Kang, 2015 [47]; *[4]* Kao, 2012 [48]; *[5]* Luo, 2017 [44]; *[6]* Otterbach, 2010 [49]; *[7]* Park, 2017 [50]; *[8]* Qin, 2016 [51]; *[9,20,23,29]* Sato, 2018 [52]; *[10]* Sekine, 2014 [53]; *[11]* Smith, 2019 [54]; *[12,14,15,21,22,25–27,30]* Thapa, 2018 [55]; *[13]* Yoshida, 2013 [56]; *[16]* Chae, 2015 [57]; *[17]* Liu, 2013 [58]; *[18,28]* Peng, 2016 [59]; *[19]* Rubenwolf, 2015 [60]. Italicized numbers under the heading "*[ref]*" in this Figure correspond to the citations designated in this figure legend.

The finite number of publications in this diverse field preclude an exhaustive comparison of all classes of AQPs across all cancer types. In parallel with the systematic review data, an independent analysis of AQP RNA expression levels by cancer type was carried out for glioma, colorectal, lung, breast, ovarian and endometrial cancers, using RNAseq transcriptomic data compiled from the Human Protein Atlas database, to serve as a second arm of this study. Transcriptomic outcomes were compared with the results of the systematic review, as summarized in the sections below, to identify corroborating lines of evidence, inconsistent findings and interesting gaps in knowledge that could merit future research.

The three limitations of this study are as follows: (i) Data from diverse experimental methods and models were merged from the published papers that were included in the systematic analysis; (ii) the number of published studies to date regarding aquaporin channels in cancers is limited; and (iii) RNAseq transcriptomic data are based on human biopsy samples taken at random locations in excised human tumor masses, and thus do not necessarily reflect a full array of gene transcripts that might exist in heterologous assemblies of cancers cells located in different regions of tumor masses. In sum, these limitations means that AQPs which are identified as important for cancer progression in one arm of analysis here might not necessary be mirrored perfectly by data compiled in the complementary analysis, and that absence of evidence does not rule out potential roles for these classes of AQP channels in cancers that are yet to be investigated.

2.1. AQPs in Gliomas

The human brain consists of 100 billion neurons and one trillion glial cells, on average [61]. Localized in astrocyte end feet throughout the brain and spinal cord, AQP4 enables central nervous system fluid homeostasis and promotes maintenance of the blood–brain barrier [62]. AQP1 normally is expressed in the choroid plexus epithelium, where it contributes to cerebral spinal fluid secretion by mediating water flux from blood to brain [63,64], but it is otherwise not abundant in healthy brain tissues. AQP9, a channel permeable to a variety of organic substrates, including lactate, glycerol and other solutes, is expressed at low levels in glia and neurons, where it is speculated to play a role in energy metabolism, though details remain to be clarified [65].

Upregulation of AQP1 and AQP4 protein and RNA has been the major focus of papers published in the glioma field (Table 2), with additional work identifying possible involvement of AQP9. AQP1 overexpression has been observed in diverse types of gliomas, such as glioblastoma, astrocytomas, oligodendrogliomas, ependymomas and glioastrocytomas; the levels of expression have been reported to correlate with the grade of malignancy and invasiveness of the tumors [66–72]. Glioma invasiveness has been linked to AQP1 overexpression [73], which is greater in migrating cells than in the tumor core [68]. Dexamethasone, which promotes AQP1 transcription, increases the invasiveness of glioma cells [74,75].

Table 2. Publications on AQPs in glioma, classified by research approach.

AQP Class	# Pubs	Research Approach (with Cited Papers in Each Category)	
		Expression	Function
AQP1	21	[49,66–84]	[73–75,77,81,83]
AQP2	1	[79]	NIF
AQP3	2	[79,85]	[85]
AQP4	25	[78,79,81,82,84,86–105]	[81,87–90,102,103]
AQP5	2	[79,106]	[106]
AQP6	1	[79]	NIF
AQP7	1	[79]	NIF
AQP8	2	[79,107]	NIF
AQP9	5	[79,104,108–110]	[110]
AQP10	1	[79]	NIF
AQP11	1	[79]	NIF

NIF: none identified in final set of papers evaluated. "# Pubs" refers to the number of publications that met criteria for inclusion in the systematic review of literature; see Results text for more details.

AQP4 upregulation and redistribution in glioblastoma [82,93,95,100,105,111] has been suggested to contribute to tumor-associated edema observed by magnetic resonance imaging [91,112,113], and conversely enhance clearance of excess fluid [103]. Genetic deletion of AQP4 impairs cell migration, actin polymerization and apoptosis [89,90]. Downregulation of AQP4 expression in glioma by pentamidine and temozolomide promoted apoptosis and inhibited cell migration, which could

be a potential treatment for glioma [87,88]. The incidence of epileptiform seizures in glioma patients correlated with increased membrane levels of AQP4 protein, though transcript levels were not altered [114], raising the important point that not just translational synthesis but also subcellular localization of proteins is essential for deciphering functional outcomes. AQP4 isoforms are able to form heterotetramers, which can turn assemble into higher-order structures called orthogonal arrays of particles, indicating a link to actin cytoskeleton [115]. AQP9 is not highly expressed in normal brain; however, increased levels observed in human glioma were correlated with pathological grade [108] and are proposed to promote cell invasiveness via an AKT signaling pathway [110].

Separate analyses of transcriptomic data from the Human Protein Atlas pathology database complemented the systematic literature review that was aimed at assessing links between AQP transcript levels and cancer risk outcomes. Transcript levels in human gliomas ranged up to high levels for AQP1 and AQP4 (Figure 3A), whereas other classes of AQPs generally showed slightly lower levels, or no difference, as compared to overall AQP median values. The risk of death for glioma patients after diagnosis (Figure 4A) showed moderate possible associations with transcript levels for AQPs 1, 2, 3, 6, 9 and 11 (HRs ranging from 1.2 to 1.6), but the hazard ratio was almost doubled for patients with AQP5 transcript levels exceeding the median value (HR1.9). AQP4 was not associated with a negative effect (HR 0.9), perhaps not surprising given that AQP4 is ubiquitously expressed at high levels in normal glia. There is a substantial gap in knowledge on possible roles of AQPs 5 and 9, which showed the highest hazard ratios but are comparatively underexplored in published work, suggesting an area that merits future study in glioma research.

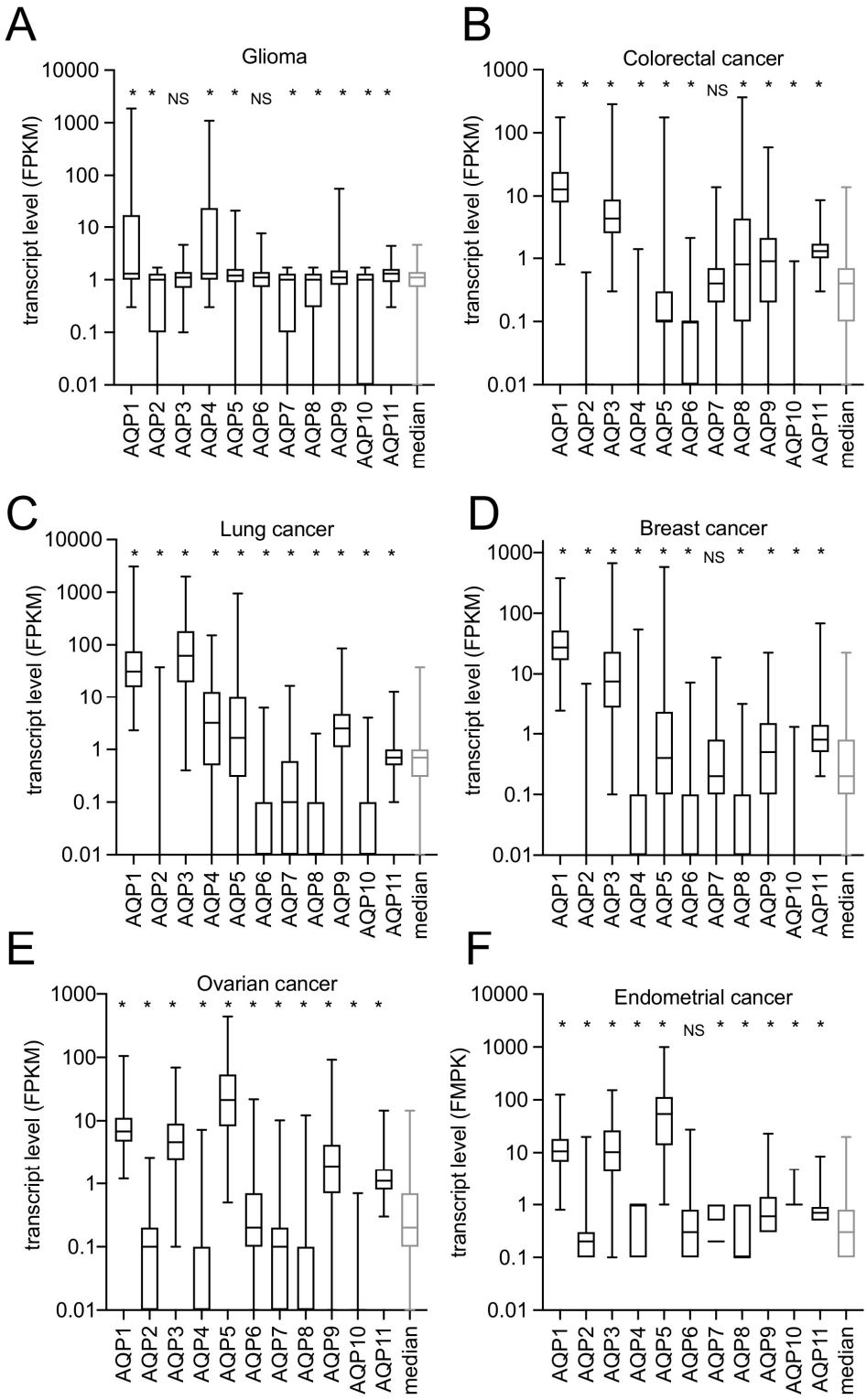

Figure 3. Quantitative transcript levels in human cancer biopsies, calculated as "fragments per kilobase of exon per million reads mapped" (FPKM). Data from the RNAseq transcriptomic database (Human Protein Atlas, https://www.proteinatlas.org), summarized by AQP class, are shown as box plots for six cancer types (**A**–**F**, as indicated). Boxes show 50% of data points; error bars show the full range; horizontal bars show median values. Median transcript levels are average FPMK values for all classes of AQPs (1–11) within each cancer type. * $p < 0.05$ as compared with the median values (Mann Whitney U-test); NS is not significant.

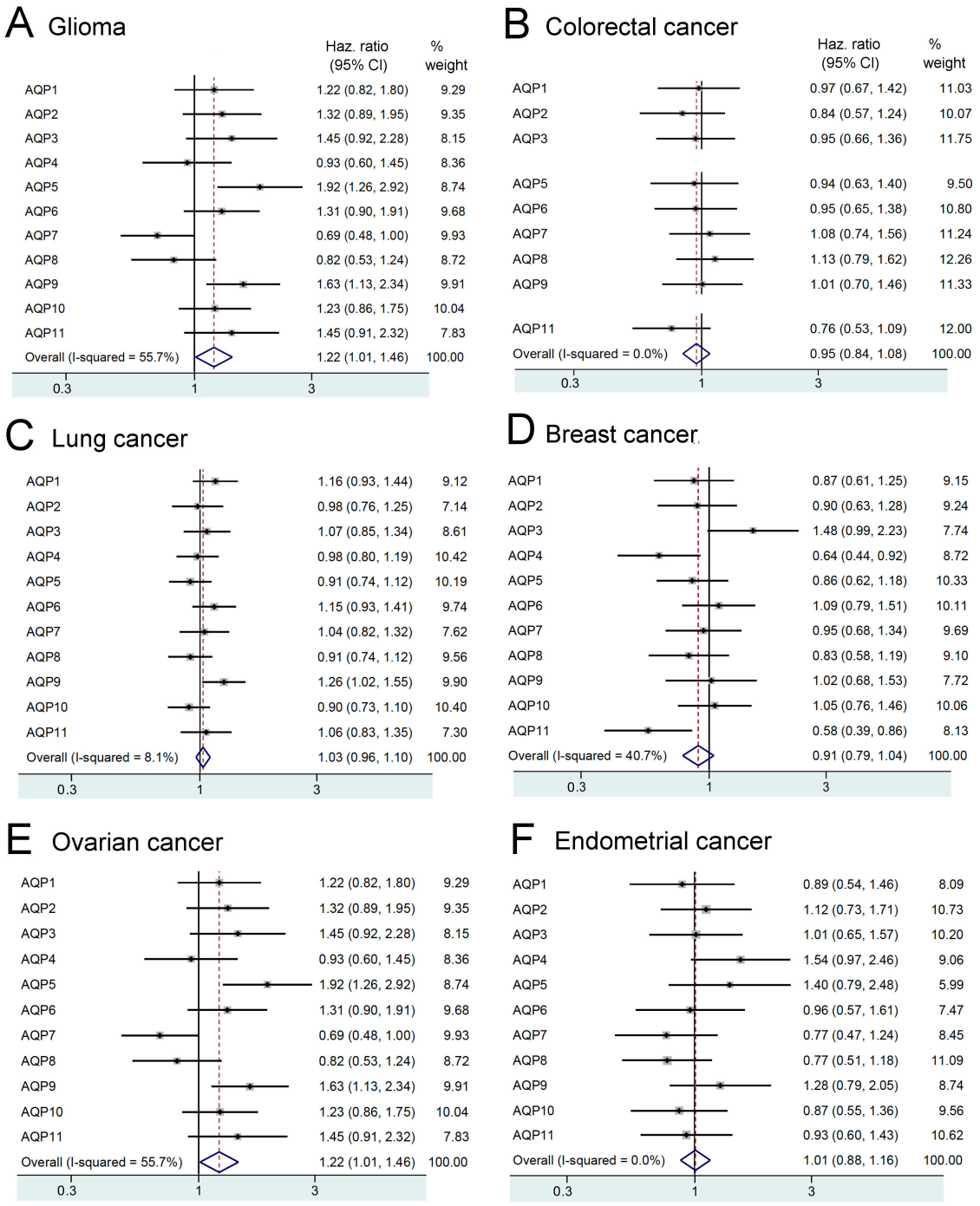

Figure 4. Increases and decreases in the risk of death for cancer patients show patterns associated with the upregulation of transcript levels for different classes of AQPs, depending on cancer type. Forest plots depict associations between survival time and median RNA expression compiled for multiple samples (patient data from the Human Protein Atlas) for six types of cancers (**A**–**F**). Hazard ratios estimate the magnitude of the effect, calculated using an interactive algorithm on the Atlas site that divides populations into high and low expression groups by median FPKM values. The vertical line indicates no effect (odds ratio 1.0); horizontal lines indicate 95% confidence interval (CI); the percent weight reflects the power of the analysis (increased by higher n values and tighter confidence intervals).

2.2. AQPs in Colon Cancer

Colorectal (bowel) cancer initiates from small noncancerous polyps inside the colon and mainly affects older adults [39]. In normal colon tissue, AQPs 1, 3, 4, 7 and 8 are the predominant isoforms, which are responsible for water absorption [116]. The expression and functions of AQP1 and AQP5 have been the main focus of papers published in the colorectal cancer field (Table 3). AQP1 is upregulated from early through late stages of colorectal carcinogenesis, and expression levels have been suggested to correlate with tumor invasiveness, prompting classification of AQP1 as a negative prognostic indicator of patient survival [56,117,118]. Molecular knockdown and pharmacological inhibition of AQP1 in colon cancer cells significantly impaired migration, supporting AQP1 as a candidate target for colon cancer therapy [118–123]. Effects on motility could arise from AQP1-associated effects on actin organization via RhoA and Rac signaling pathways [123]. Alternatively, the role of AQP1 in colon cancer might depend on a dual water and ion channel function suggested to promote lamellipodial extension and cell migration [5,12,123]. AQP5 similarly has been proposed as a prognostic biomarker for colorectal cancer, with AQP5 levels found to be proportional to numbers of circulating tumors cells [124–126] and risk of liver metastases [126]. Cell proliferation induced by increased AQP5 involved Ras-MAPK signaling pathways [126]; conversely, AQP5 knockdown inhibited proliferation and triggered apoptosis [127,128]. AQP3 has been suggested to modulate tumor differentiation in colon cancer patients via the EGFR pathway, but its role remains to be defined [129]. Glycerol-permeable AQP3 in other tissues is involved in nutrient uptake and metabolism [28], and it could contribute similarly in some cancers.

Table 3. Publications on AQPs in colon cancers, classified by research approach.

AQP Class	# Pubs	Research Approach (with Cited Papers in Each Category)	
		Expression	Function
AQP1	11	[56,123]	[119–123,130]
AQP2	0	NIF	NIF
AQP3	2	[129,131]	[129]
AQP4	0	NIF	NIF
AQP5	11	[124–129,131–135]	[126–129,132–135]
AQP6	0	NIF	NIF
AQP7	0	NIF	NIF
AQP8	1	[136]	[136]
AQP9	3	[137–139]	[138], [139]
AQP10	0	NIF	NIF
AQP11	0	NIF	NIF

NIF: none identified in final set of papers evaluated. "# Pubs" refers to the number of publications that met criteria for inclusion in the systematic review of literature; see Results text for more details.

In related work, levels of AQPs 1, 5 and 9 protein expression in biopsied samples have been associated with the effectiveness of chemotherapy applied post-surgery in patients with Stages II and III colorectal carcinoma, suggesting another use for AQPs as biomarkers in personalized medicine [140]. Genetic knockdown of AQP5 increased sensitivity to chemotherapy and downregulated p38 MAPK signaling in colon cancer cells [127,134]. Conversely, colon cancer patients non-responsive to adjuvant chemotherapy were more likely to have low AQP9 expression [137,138].

In agreement with one of the studies from the systematic review summary shown in Figure 2 AQP transcript data extracted from the Human Protein Atlas database indicated elevation of AQP1 RNA in colorectal cancers (Figure 3B), as referenced to overall median AQP. AQP3 transcript levels also appeared high, suggesting a gap in knowledge with regard to a possible role in colon cancer. However, the patterns of expression of AQPs showed no association with survival time for any of the classes of AQPs (Figure 4B), suggesting that although classes of AQPs might enable important aspects of cancer

progression, they fall short of serving as robust negative prognostic indicators for survival in colorectal cancer patients, based on data available to date.

2.3. AQPs in Lung Cancer

Lung cancers can be divided into two main groups, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), which can be further subdivided into adenocarcinoma, squamous cell carcinoma and large-cell carcinoma [141–143]. In lung tissues, AQP 1 protein normally is expressed in microvascular endothelia, and AQP3 and AQP4 are in airway epithelia [144]. Overexpression of AQP1, AQP3 and AQP5 has been the major focus of papers published in the lung cancer field (Table 4). AQP1 protein and RNA expression, upregulated in lung adenocarcinoma and bronchoalveolar carcinoma (but not in lung squamous cell carcinoma), was correlated with a high risk of postoperative metastasis and low disease-free survival rates, and therefore suggested to be a prognostic factor for stage categories and histologic differentiation of lung cancers [46,142,143,145,146]. Poor survival in asbestos-related mesothelioma similarly was associated with higher AQP1 levels identified in neoplastic tissues by immunocytochemistry [45,48]. Interestingly, chemotherapy appeared to result in increased AQP1 expression [147], which might, in theory, cause a counterproductive boost in cancer recurrence by enhancing invasiveness. Transfection of AQP1 into lung cancer cells enhanced proliferation in vitro [145]; AQP1 overexpression in capillary endothelia of lung adenocarcinoma and mesothelioma tumors promoted angiogenesis, which would facilitate cancer growth and spread [146]. Levels of AQP3 in lung adenocarcinoma were correlated with tumor differentiation and clinical stage [129]. Increased AQP3 also promoted angiogenesis in lung cancer through HIF-2α–VEGF, and invasion via AKT–MMP pathways [148]. In NSCLC patients, high levels of AQP4 did not correlate with poorer survival [101]; in contrast, AQP5 overexpression was associated with unfavorable outcomes [149–151]. Genetic knockdown of AQP5 in cell lines reduced migration [152,153], whereas upregulation of AQP5 was associated with activated epidermal growth factor receptor (EGFR), extracellular receptor kinase (ERK1/2) and p38 mitogen-activated protein kinase (p38 MAPK) signaling pathways, to facilitate proliferation and migration [154]. AQP3 coexpression with AQP5 was linked to poor survival, suggesting that combined detection of markers might strengthen prognostic predictive value [58].

Table 4. Publications on AQPs in lung cancers, classified by research approach.

AQP Class	# Pubs	Research Approach (with Cited Papers in Each Category)	
		Expression	Function
AQP1	12	[46,99,117,142,143,145–147,155–158]	[99,145,156–158]
AQP2	0		NIF
AQP3	8	[142,148,155,159–163]	[159,161,162]
AQP4	2	[101,155]	NIF
AQP5	13	[46,142,147,149–155,160,164,165]	[149,152–154,164,165]
AQP6	0	NIF	NIF
AQP7	0	NIF	NIF
AQP8	0	NIF	NIF
AQP9	1	[166]	[166]
AQP10	0	NIF	NIF
AQP11	1	[167]	NIF

NIF: none identified in final set of papers evaluated. "# Pubs" refers to the number of publications that met criteria for inclusion in the systematic review of literature; see Results text for more details.

Consistent with systematic review results in Figure 2 showing a high hazard ratio for AQP1 (HR 4), increased transcript levels for AQP1 were observed in lung cancer biopsies (Figure 3C). A parallel increase in levels of AQP3 could point to a gap in knowledge regarding a possible role in lung cancer. However, the hazard ratio calculations for overall survival time of patients with lung cancer showed no convincing associations with expression levels of any classes of AQPs, apart from a possible

small increase in hazard (HR 1.3) with AQP9 (Figure 4C), suggesting another area for future inquiry. The potential clinical value of any of the classes of AQPs as reliable prognostic indicators in lung cancer thus remains unclear at present.

2.4. AQPs in Breast Cancer

Breast cancer adenocarcinoma begins with mutated cells in the milk ducts or lobules [168]. Upregulation of AQPs 1, 3 and 5 has been the major focus of papers published in the breast cancer field (Table 5). AQP1 upregulation in breast cancer, induced by estrogen [169] and negatively regulated by microRNA-320 [170], was correlated with prognoses of poor survival for breast cancer patients [51,171]. High levels of AQP1 protein were associated with the most aggressive subtypes of basal-like breast carcinomas [49]. Protein levels of AQP1 similarly were correlated with poor outcomes, high rates of recurrence and invasiveness in other cancers, including prostate adenocarcinoma [50], biliary tract carcinoma [172] and gastric cancer [55]. AQP3 is upregulated in the early stages of breast cancer, in response to fibroblast growth factor via FGFR–PI3K or FGFR–ERK signaling pathways, and estrogen [173,174]. High AQP3 expression is correlated with low patient survival rates post-surgery, suggesting value as a prognostic marker [47,57]. Increased levels of AQP3 channels, mediating H_2O_2 transport and inducing CXCL12- cell signaling and migration, could promote breast cancer metastasis [174,175]. Following a similar pattern, AQP5 upregulation by estrogen in breast cancer patients from early stages correlated with reduced survival times, suggesting AQP5 also was a prognostic marker [176,177]. Knockdown of AQP5 activated the MAPK signaling pathway, reducing cell invasiveness and proliferation, and enhanced the chemosensitivity of breast cancer cells, suggesting AQP5 is of interest as a biomarker and a pharmacological target [178,179].

Table 5. Publications on AQPs in breast cancer, classified by research approach.

AQP Class	# Pubs	Research Approach (with Cited Papers in Each Category)	
		Expression	Function
AQP1	6	[51,117,171,180,181]	[51,175,181]
AQP2	1	[180]	NIF
AQP3	8	[47,57,85,173–175,180]	[85,159,173–175]
AQP4	2	[180,182]	NIF
AQP5	7	[176–180,183,184]	[178,179,183]
AQP6	1	[180]	NIF
AQP7	1	[180]	NIF
AQP8	1	[180]	NIF
AQP9	2	[85,180]	[85]
AQP10	1	[180]	NIF
AQP11	1	[180]	NIF

NIF: none identified in final set of papers evaluated. "# Pubs" refers to the number of publications that met criteria for inclusion in the systematic review of literature; see Results text for more details.

Results from the systematic review shown in Figure 2 indicated that increased AQPs 1 and 3 protein and RNA expression levels correlated with increased risk of death with hazard ratios of 2.9 and 3.1, respectively. In agreement, transcriptomic analyses from the Human Protein Atlas database showed distinctly higher levels for AQP1 and AQP3 transcripts (Figure 3D), with AQPs 5, 7, 9 and 11 also showing possible moderately increased levels, as compared with overall median AQP levels in breast cancer biopsies. However, apart from AQP3 with a hazard ratio of 1.5, the patterns of upregulated AQP expression were not correlated with reduced survival rates in breast cancer patients (Figure 4D), based on data available to date. Interestingly, increased levels of AQPs 4 and 11 were linked to longer overall survival times (HR 0.6 in both), suggesting some classes of AQP subtypes might have an anticancer potential yet to be defined.

2.5. AQPs in Ovarian Cancer

AQPs 1, 2, 3 and 4 channels are normally expressed in ovary [185,186]. Overexpression of AQPs 1, 3, 5 and 9 protein has been observed in ovarian tumors [52], and has been the major focus of papers published in the ovarian cancer field (Table 6). AQP1 protein expression was upregulated in the late stages of ovarian tumors, but the positive or negative associations with survival rates of patients depended on the cancer subtype category [52,187,188]. AQP3 upregulation by EGF promoted cell migration in an ovarian cancer cell line, which was inhibited by curcumin [189]. Inhibition of AQP3 by Auphen inhibited proliferation of xenografted hepatocarcinoma cells in mice [59,190]. Conversely, in patients with urothelial or bladder carcinomas, high levels of AQP3 protein and RNA were associated with better progression-free survival [60,191], suggesting that the roles of AQP classes are likely to depend on the cancer subtype. Multiple studies have reported direct correlations of AQP5 expression levels with tumor grade, lymph node metastasis and poor prognoses, suggesting AQP5 could be a prognostic factor for ovarian cancer [52,192,193]. AQP5 expression level was also associated with the sensitivity of ovarian cancer cells to chemotherapy [194]. AQP6 and AQP9 were reported to be downregulated, whereas AQP8 was unchanged, in ovarian cancer, but their roles remain to be determined [52,195].

Table 6. Publications on AQPs in ovarian cancer, classified by research approach.

AQP Class	# Pubs	Research Approach (with Cited Papers in Each Category)	
		Expression	Function
AQP1	6	[52,117,188,194,196,197]	[188]
AQP2	3	[188,197]	[188]
AQP3	8	[52,85,187–189,197,198]	[85,188,189]
AQP4	3	[188,197]	[188]
AQP5	8	[52,188,192–194,197,199]	[188,194,199]
AQP6	4	[120,188,197]	[188]
AQP7	4	[187,188,197]	[188]
AQP8	4	[188,195,197]	[188]
AQP9	6	[52,85,187,188,197]	[85,188]
AQP10	2	[188]	[188]
AQP11	0	NIF	NIF

NIF: none identified in final set of papers evaluated. "# Pubs" refers to the number of publications that met criteria for inclusion in the systematic review of literature; see Results text for more details.

Largely consistent with the systematic review results (Figure 2) which indicated high hazard ratios for AQP1 (HR 1.4), AQP5 (HR 1.6) and AQP9 (HR 1.9), though interestingly not AQP3, transcript levels obtained from the Human Protein Atlas database suggested high levels of AQPs 1, 3, 5 and 9 in ovarian cancer biopsies (Figure 3E), as well as a possible increase in AQP11. Increased transcript levels correlated with reduced overall survival times for ovarian cancer patients across the panel of AQPs (HRs 1.2 to 1.9), with the exception of AQPs 4, 7 and 8 (Figure 4E). Conversely, increased levels of AQP7 and AQP8 expression correlated with longer survival times, suggesting a possible protective role in cancer that could be analogous to effects of AQPs 4 and 11 in breast cancer, as noted above.

2.6. AQPs in Endometrial Cancer

The roles of AQPs in endometrial cancer and other less-well-studied cancers remain a gap in knowledge in the field (Table 7). Endometrial cancer arises from tissue lining the uterus (the endometrium) and accounts for about 95% of uterine cancers. Protein and RNA for AQPs 1, 2, 3, 5, 7 and 9 are normally expressed in endometrium, in which the AQPs are thought to be involved in fluid exchange and estrogen-mediated regulatory effects [200–206]. AQP1 expression in endometrial cancer has been correlated with histologic grade, extent of myometrial invasion and the likelihood of extrauterine metastasis [207], but the functional role of AQP1 in this tissue remains to be defined.

Table 7. Publications on AQPs in other cancer types.

Cancer Type	Type of AQP	Cited References
Biliary tract cancer	AQP1	[53]
	AQP5	[172]
Bladder cancer	AQP1	[208]
	AQP3	[60]
Bone cancer	AQP3	[209]
Cervical cancer	AQP1	[154,210–214]
	AQP3	[211,213,214]
	AQP4	[213]
	AQP5	[213,215,216]
	AQP8	[210,213,214,217–219]
Endometrial cancer	AQP1	[207]
	AQP2	[220]
Gallbladder cancer	AQP5	[221]
Gastric cancer	AQP1-11	[55]
	AQP2	[222]
	AQP3	[223–227]
	AQP5	[228]
Leukemia	AQP5	[229]
	AQP8	[230]
	AQP9	[231–234]
Liver cancer	AQP1	[144,235]
	AQP3	[59,196,236–238]
	AQP5	[238–241]
	AQP7	[237]
	AQP9	[59,196,237,242–244]
Melanoma, cutaneous	AQP1	[245,246]
Mesothelioma	AQP1	[45,48,247–252]
Esophageal cancer	AQP3	[58]
	AQP4	[253]
	AQP5	[58,254]
	AQP8	[255]
Pancreatic cancer	AQP1	[256]
	AQP3	[256,257]
Prostate cancer	AQP1	[50,117,258,259]
	AQP2	[260]
	AQP3	[258,261,262]
	AQP5	[263]
Renal cancer	AQP1	[264–271]
	AQP5	[272]
Skin cancer	AQP1	[273–276]
	AQP3	[161,277–279]
Squamous cell carcinoma, oral	AQP3	[280]
Squamous cell carcinoma, pharyngeal	AQP1, 5	[281]
Squamous cell carcinoma, tongue	AQP3, 5	[162]
Thyroid cancer	AQP3, 4	[282]
Urothelial Carcinoma	AQP1	[283]
	AQP3	[197,284]

Data from the Human Protein Atlas database indicated that AQPs 1, 3 and 5 showed relatively higher levels of transcripts in endometrial cancer biopsies, as compared to other classes (Figure 3F). Increased transcript levels for AQP5 were correlated with poor survival, with hazard ratios of 1.4 in endometrial cancers (Figure 4F). Increased hazard ratios seen for AQP4 (HR1.5) and perhaps AQP9 (HR1.3) remain a gap in knowledge in the field. Future research could explore possible roles of classes of AQPs in endometrial and other cancers.

3. Discussion

Patterns of upregulation of specific classes of aquaporins were repeated for clusters of cancers, and they showed associations with the risk of death. The most frequent pattern linked to pathological severity involved AQPs 1, 3 and/or 5 as negative indicators for multiple cancer types. In glioblastoma, lung and ovarian cancers, AQP9 also appeared to be a candidate of interest for cancer severity. Conversely, a fascinating observation was that higher levels of AQPs 7 and 8 were associated with lower hazard ratios in glioblastoma and ovarian cancer; and AQP11 appeared to have a beneficial influence in breast and colorectal cancers. Possible protective mechanisms remain unexplored, but could involve possible roles, for example, for AQPs 8 or 9, in promoting the cell volume loss preceding apoptosis [35], or for AQPs 7 or 11, in enabling glycerol or hydrogen peroxide transport [285]. Although fundamental mechanisms of aquaporins both for promoting cancer metastasis and in exerting protective influences remain to be defined, results here support the hypothesis that overexpression of selected classes of AQPs differentially augments cancer progression, depending on the cancer subtype. Patterns of aquaporin expression also have been linked with differences in sensitivity to chemotherapy treatments, suggesting possible roles as biomarkers for designing targeted treatments. AQP5, in particular, underpinned a recurring theme as a biomarker in diverse cancers, including colon, breast and ovarian. AQP channels localized in the leading edges of migrating cancer cells are positioned to enhance cell migration as part of the volume regulatory engine driving process extension. Aquaporins merit investigation as cancer-specific therapeutic targets. Pending progress in defining subtype-selective pharmacological modulators of AQPs, tailored combinations of agents could be used to target specific cancer types and greatly expand clinical options for cancer treatment.

4. Materials and Methods

4.1. Systematic Review Protocol and Inclusion Criteria

Data included in the systematic analysis included all primary research published between 1 January 1990 and 1 January 2019 that was indexed in PubMed or Embase (OVID version) online databases and reported to have investigated aquaporins and cancers. Papers included work using biopsies, cancer cell lines, animal models and human patient cohort studies. Lists of the search keywords used for querying the online databases are summarized in Table 1.

For positive hits identified using the search keywords, titles and abstracts were screened to determine whether the retrieved studies met intended criteria. Review articles, conference abstracts and studies that did not have a focus on aquaporins were excluded. For studies that met the selection criteria, complete published papers were obtained and evaluated (flowchart in Figure 1; extracted data summary in Table S1).

4.2. Forest Plot Analyses

Hazard ratios for overall survival rates in people with cancers were extracted from data in the final papers collected in the comprehensive literature search. Forest plots utilizing the random effects model were generated to assess hazard ratios for each class of AQPs, using Stata software (Stata software, StataCorp, College Station, TX, USA).

Overall survival times of people with cancers were obtained from the Human Protein Atlas database, available at https://www.proteinatlas.org/humanproteome/pathology [286,287]. Data from

patient biopsy samples were classified into high or low expression groups (above or below median) for AQP classes 1 to 10, based on RNAseq data quantified as "fragments per kilobase of exon per million reads mapped" (FPKM) values for AQP transcript levels. RNAseq data were used to calculate hazard ratios for each class of AQPs classified by the type of cancer, using GraphPad Prism 8 (San Diego, CA, USA). Forest plots based on the random effects model were generated to determine hazard ratios for each class of AQPs, using Stata software.

4.3. Statistical Analyses

Box plots were generated by using GraphPad Prism 8 software to summarize transcript levels for classes of AQPs measured in samples of human glioma, colon cancer, lung cancer, breast cancer, ovarian cancer and endometrial cancer biopsies, compiled from Human Protein Atlas transcriptomic data. The median values for the transcript levels for all AQP classes in individual patient samples were used as the point of reference for statistical comparisons. Statistically significant outcomes determined by the non-parametric Mann–Whitney U tests (with GraphPad Prism 8) are reported as * $p < 0.05$. NS is not significant.

5. Conclusions

Overexpression of specific classes of AQPs is consistently observed in clinical and preclinical studies of cancers. Different classes of AQPs have been linked to properties of migration, invasion, proliferation and angiogenesis, depending on the cancer type. Analyses here provide evidence that the upregulation of certain AQPs is negatively associated with survival time for people with cancers. AQPs 1, 3, 5 and 9 in particular are associated with reduced survival for cases of glioma, ovarian and endometrial cancers, via both direct and indirect mechanisms yet to be defined. High hazard ratios were noted for AQP5 and AQP9 in glioma and ovarian cancers; more research is needed on their possible pathophysiological roles. Not all classes of AQPs were associated with worse outcomes; on the contrary, AQPs 7, 8 and 11 are intriguing as potential components of protective mechanisms against some cancer types, framing a novel gap in knowledge in the field. In summary, results here provide a logical rationale for evaluating AQPs as targets for tailored cancer therapies. Small molecule inhibitors of AQPs are being developed, though they remain to be advanced to clinical trials. Research to define and optimize AQP pharmacological agents, and studies to explore the mechanisms of these channels in cancer growth and progression, are needed to address a clinically important but untapped area of work.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6694/12/7/1911/s1, Table S1: Extracted data (Summary details for all publications analysed in the systematic review section of this work).

Author Contributions: Conceptualization, P.H.C. and A.J.Y.; methodology, P.H.C., J.B. and A.J.Y.; formal analysis, P.H.C.; investigation, P.H.C.; writing—original draft preparation, P.H.C. and A.J.Y.; writing—review and editing, P.H.C., J.B. and A.J.Y.; supervision, J.B. and A.J.Y.; project administration and funding Acquisition, A.J.Y. All authors have read and agreed to the published version of the manuscript.

Funding: Funding was provided by the Australian Research Council (grant ARC_DP190101745).

Acknowledgments: We thank the University of Adelaide Research Librarian Vikki Langton for training and assistance in systemic review methods.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Dubyak, G.R. Ion homeostasis, channels, and transporters: An update on cellular mechanisms. *Adv. Physiol. Educ.* **2004**, *28*, 143–154. [CrossRef] [PubMed]
2. Litan, A.; Langhans, S.A. Cancer as a channelopathy: Ion channels and pumps in tumor development and progression. *Front. Cell. Neurosci.* **2015**, *9*, 86. [CrossRef] [PubMed]
3. King, L.S.; Kozono, D.; Agre, P. From structure to disease: The evolving tale of aquaporin biology. *Nat. Rev. Mol. Cell Biol.* **2004**, *5*, 687–698. [CrossRef] [PubMed]

4. Nico, B.; Ribatti, D. Aquaporins in tumor growth and angiogenesis. *Cancer Lett.* **2010**, *294*, 135–138. [CrossRef] [PubMed]
5. Anthony, T.L.; Brooks, H.L.; Boassa, D.; Leonov, S.; Yanochko, G.M.; Regan, J.W.; Yool, A.J. Cloned human aquaporin-1 is a cyclic GMP-gated ion channel. *Mol. Pharm.* **2000**, *57*, 576–588. [CrossRef] [PubMed]
6. McCoy, E.; Sontheimer, H. Expression and function of water channels (aquaporins) in migrating malignant astrocytes. *Glia* **2007**, *55*, 1034–1043. [CrossRef] [PubMed]
7. Hu, J.; Verkman, A.S. Increased migration and metastatic potential of tumor cells expressing aquaporin water channels. *FASEB J.* **2006**, *20*, 1892–1894. [CrossRef]
8. De Ieso, M.L.; Yool, A.J. Mechanisms of Aquaporin-Facilitated Cancer Invasion and Metastasis. *Front. Chem.* **2018**, *6*, 135. [CrossRef]
9. Papadopoulos, M.C.; Saadoun, S. Key roles of aquaporins in tumor biology. *Biochim. Biophys. Acta* **2015**, *1848*, 2576–2583. [CrossRef]
10. Yool, A.J.; Brown, E.A.; Flynn, G.A. Roles for novel pharmacological blockers of aquaporins in the treatment of brain oedema and cancer. *Clin. Exp. Pharm. Physiol.* **2009**, *37*, 403–409. [CrossRef]
11. Wang, J.; Feng, L.; Zhu, Z.; Zheng, M.; Wang, D.; Chen, Z.; Sun, H. Aquaporins as diagnostic and therapeutic targets in cancer: How far we are? *J. Transl. Med.* **2015**, *13*, 96. [CrossRef]
12. De Ieso, M.L.; Pei, J.V.; Nourmohammadi, S.; Smith, E.; Chow, P.H.; Kourghi, M.; Hardingham, J.E.; Yool, A.J. Combined pharmacological administration of AQP1 ion channel blocker AqB011 and water channel blocker Bacopaside II amplifies inhibition of colon cancer cell migration. *Sci. Rep.* **2019**, *9*, 12635. [CrossRef] [PubMed]
13. Ishibashi, K.; Hara, S.; Kondo, S. Aquaporin water channels in mammals. *Clin. Exp. Nephrol.* **2009**, *13*, 107–117. [CrossRef] [PubMed]
14. Finn, R.N.; Chauvigne, F.; Hlidberg, J.B.; Cutler, C.P.; Cerda, J. The lineage-specific evolution of aquaporin gene clusters facilitated tetrapod terrestrial adaptation. *PLoS ONE* **2014**, *9*, e113686. [CrossRef] [PubMed]
15. Jenq, W.; Cooper, D.R.; Bittle, P.; Ramirez, G. Aquaporin-1 expression in proximal tubule epithelial cells of human kidney is regulated by hyperosmolarity and contrast agents. *Biochem. Biophys. Res. Commun.* **1999**, *256*, 240–248. [CrossRef] [PubMed]
16. Kitchen, P.; Day, R.E.; Salman, M.M.; Conner, M.T.; Bill, R.M.; Conner, A.C. Beyond water homeostasis: Diverse functional roles of mammalian aquaporins. *Biochim. Biophys. Acta* **2015**, *1850*, 2410–2421. [CrossRef] [PubMed]
17. Yool, A.J. Functional domains of aquaporin-1: Keys to physiology, and targets for drug discovery. *Curr. Pharm. Des.* **2007**, *13*, 3212–3221. [CrossRef] [PubMed]
18. Yool, A.J.; Campbell, E.M. Structure, function and translational relevance of aquaporin dual water and ion channels. *Mol. Asp. Med.* **2012**, *33*, 443–561. [CrossRef]
19. Ishibashi, K. New members of mammalian aquaporins: AQP10-AQP12. *Handb. Exp. Pharmacol.* **2009**, *190*, 251–262. [CrossRef]
20. Almasalmeh, A.; Krenc, D.; Wu, B.; Beitz, E. Structural determinants of the hydrogen peroxide permeability of aquaporins. *FEBS J.* **2014**, *281*, 647–656. [CrossRef]
21. Wu, B.; Beitz, E. Aquaporins with selectivity for unconventional permeants. *Cell Mol. Life Sci.* **2007**, *64*, 2413–2421. [CrossRef] [PubMed]
22. Herrera, M.; Garvin, J.L. Novel role of AQP-1 in NO-dependent vasorelaxation. *Am. J. Physiol. Ren. Physiol.* **2007**, *292*, F1443–F1451. [CrossRef] [PubMed]
23. Wang, Y.; Tajkhorshid, E. Nitric oxide conduction by the brain aquaporin AQP4. *Proteins* **2010**, *78*, 661–670. [CrossRef] [PubMed]
24. Musa-Aziz, R.; Chen, L.M.; Pelletier, M.F.; Boron, W.F. Relative CO2/NH3 selectivities of AQP1, AQP4, AQP5, AmtB, and RhAG. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5406–5411. [CrossRef] [PubMed]
25. Zwiazek, J.J.; Xu, H.; Tan, X.; Navarro-Rodenas, A.; Morte, A. Significance of oxygen transport through aquaporins. *Sci. Rep.* **2017**, *7*, 40411. [CrossRef] [PubMed]
26. Galan-Cobo, A.; Ramirez-Lorca, R.; Echevarria, M. Role of aquaporins in cell proliferation: What else beyond water permeability? *Channels (Austin)* **2016**, *10*, 185–201. [CrossRef] [PubMed]
27. Calamita, G.; Perret, J.; Delporte, C. Aquaglyceroporins: Drug Targets for Metabolic Diseases? *Front. Physiol.* **2018**, *9*, 851. [CrossRef]

28. da Silva, I.V.; Rodrigues, J.S.; Rebelo, I.; Miranda, J.P.G.; Soveral, G. Revisiting the metabolic syndrome: The emerging role of aquaglyceroporins. *Cell Mol. Life Sci.* **2018**, *75*, 1973–1988. [CrossRef]
29. Clapp, C.; Martinez de la Escalera, G. Aquaporin-1: A novel promoter of tumor angiogenesis. *Trends Endocrinol. Metab.* **2006**, *17*, 1–2. [CrossRef]
30. Baetz, N.W.; Hoffman, E.A.; Yool, A.J.; Stamer, W.D. Role of aquaporin-1 in trabecular meshwork cell homeostasis during mechanical strain. *Exp. Eye Res.* **2009**, *89*, 95–100. [CrossRef]
31. Katsura, T.; Gustafson, C.E.; Ausiello, D.A.; Brown, D. Protein kinase A phosphorylation is involved in regulated exocytosis of aquaporin-2 in transfected LLC-PK1 cells. *Am. J. Physiol.* **1997**, *272*, F817–F822. [CrossRef] [PubMed]
32. Kreida, S.; Roche, J.V.; Olsson, C.; Linse, S.; Tornroth-Horsefield, S. Protein-protein interactions in AQP regulation—Biophysical characterization of AQP0-CaM and AQP2-LIP5 complex formation. *Faraday Discuss* **2018**, *209*, 35–54. [CrossRef] [PubMed]
33. Cowan, C.A.; Yokoyama, N.; Bianchi, L.M.; Henkemeyer, M.; Fritzsch, B. EphB2 guides axons at the midline and is necessary for normal vestibular function. *Neuron* **2000**, *26*, 417–430. [CrossRef]
34. Amiry-Moghaddam, M.; Frydenlund, D.S.; Ottersen, O.P. Anchoring of aquaporin-4 in brain: Molecular mechanisms and implications for the physiology and pathophysiology of water transport. *Neuroscience* **2004**, *129*, 999–1010. [CrossRef]
35. Lee, W.K.; Thevenod, F. A role for mitochondrial aquaporins in cellular life-and-death decisions? *Am. J. Physiol. Cell. Physiol.* **2006**, *291*, C195–C202. [CrossRef] [PubMed]
36. Jessica Chen, M.; Sepramaniam, S.; Armugam, A.; Shyan Choy, M.; Manikandan, J.; Melendez, A.J.; Jeyaseelan, K.; Sang Cheung, N. Water and ion channels: Crucial in the initiation and progression of apoptosis in central nervous system? *Curr. Neuropharmacol.* **2008**, *6*, 102–116. [CrossRef]
37. Jablonski, E.M.; Webb, A.N.; McConnell, N.A.; Riley, M.C.; Hughes, F.M., Jr. Plasma membrane aquaporin activity can affect the rate of apoptosis but is inhibited after apoptotic volume decrease. *Am. J. Physiol. Cell Physiol.* **2004**, *286*, C975–C985. [CrossRef] [PubMed]
38. Papadopoulos, M.C.; Saadoun, S.; Verkman, A.S. Aquaporins and cell migration. *Pflug. Arch.* **2008**, *456*, 693–700. [CrossRef]
39. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA* **2018**, *68*, 394–424. [CrossRef]
40. Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* **2015**, *136*, E359–E386. [CrossRef] [PubMed]
41. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2016. *CA* **2016**, *66*, 7–30. [CrossRef]
42. Auguste, K.I.; Jin, S.; Uchida, K.; Yan, D.; Manley, G.T.; Papadopoulos, M.C.; Verkman, A.S. Greatly impaired migration of implanted aquaporin-4-deficient astroglial cells in mouse brain toward a site of injury. *FASEB J.* **2007**, *21*, 108–116. [CrossRef] [PubMed]
43. Steeg, P.S.; Theodorescu, D. Metastasis: A therapeutic target for cancer. *Nat. Rev. Clin. Oncol.* **2008**, *5*, 206. [CrossRef] [PubMed]
44. Luo, L.M.; Xia, H.; Shi, R.; Zeng, J.; Liu, X.R.; Wei, M. The association between aquaporin-1 expression, microvessel density and the clinicopathological features of hepatocellular carcinoma. *Oncol. Lett.* **2017**, *14*, 7077–7084. [CrossRef] [PubMed]
45. Angelico, G.; Caltabiano, R.; Loreto, C.; Ieni, A.; Tuccari, G.; Ledda, C.; Rapisarda, V. Immunohistochemical Expression of Aquaporin-1 in Fluoro-Edenite-Induced Malignant Mesothelioma: A Preliminary Report. *Int. J. Mol. Sci.* **2018**, *19*, 685. [CrossRef] [PubMed]
46. Bellezza, G.; Vannucci, J.; Bianconi, F.; Metro, G.; Del Sordo, R.; Andolfi, M.; Ferri, I.; Siccu, P.; Ludovini, V.; Puma, F.; et al. Prognostic implication of aquaporin 1 overexpression in resected lung adenocarcinoma. *Interact. Cardiovasc. Thorac. Surg.* **2017**, *25*, 856–861. [CrossRef]
47. Kang, S.; Chae, Y.S.; Lee, S.J.; Kang, B.W.; Kim, J.G.; Kim, W.W.; Jung, J.H.; Park, H.Y.; Jeong, J.H.; Jeong, J.Y.; et al. Aquaporin 3 expression predicts survival in patients with HER2-positive early breast cancer. *Anticancer Res.* **2015**, *35*, 2775–2782.

48. Kao, S.C.H.; Armstrong, N.; Condon, B.; Griggs, K.; McCaughan, B.; Maltby, S.; Wilson, A.; Henderson, D.W.; Klebe, S. Aquaporin 1 is an independent prognostic factor in pleural malignant mesothelioma. *Cancer* **2012**, *118*, 2952–2961. [CrossRef] [PubMed]
49. Otterbach, F.; Callies, R.; Adamzik, M.; Kimmig, R.; Siffert, W.; Schmid, K.W.; Bankfalvi, A. Aquaporin 1 (AQP1) expression is a novel characteristic feature of a particularly aggressive subgroup of basal-like breast carcinomas. *Breast Cancer Res. Treat.* **2010**, *120*, 67–76. [CrossRef] [PubMed]
50. Park, J.Y.; Yoon, G.S. Overexpression of Aquaporin-1 is a Prognostic Factor for Biochemical Recurrence in Prostate Adenocarcinoma. *Pathol. Oncol. Res.* **2017**, *23*, 189–196. [CrossRef]
51. Qin, F.; Zhang, H.; Shao, Y.; Liu, X.; Yang, L.; Huang, Y.; Fu, L.; Gu, F.; Ma, Y. Expression of aquaporin1, a water channel protein, in cytoplasm is negatively correlated with prognosis of breast cancer patients. *Oncotarget* **2016**, *7*, 8143–8154. [CrossRef] [PubMed]
52. Sato, K.; Miyamoto, M.; Takano, M.; Furuya, K.; Tsuda, H. Different Prognostic Implications of Aquaporin-1 and Aquaporin-5 Expression among Different Histological Types of Ovarian Carcinoma. *Pathol. Oncol. Res.* **2018**, *26*, 263–271. [CrossRef] [PubMed]
53. Sekine, S.; Sawada, S.; Nagata, T.; Osawa, S.; Shibuya, K.; Yoshioka, I.; Matsui, K.; Okumura, T.; Yoshida, T.; Tsukada, K. Expression analysis of aquaporin-1(AQP-1) in human biliary tract carcinoma. *HPB* **2014**, *16*, 332. [CrossRef]
54. Smith, E.; Tomita, Y.; Palethorpe, H.M.; Howell, S.; Nakhjavani, M.; Townsend, A.R.; Price, T.J.; Young, J.P.; Hardingham, J.E. Reduced aquaporin-1 transcript expression in colorectal carcinoma is associated with promoter hypermethylation. *Epigenetics* **2019**, *14*, 158–170. [CrossRef]
55. Thapa, S.; Chetry, M.; Huang, K.; Peng, Y.; Wang, J.; Wang, J.; Zhou, Y.; Shen, Y.; Xue, Y.; Ji, K. Significance of aquaporins' expression in the prognosis of gastric cancer. *Biosci. Rep.* **2018**, *38*, BSR20171687. [CrossRef] [PubMed]
56. Yoshida, T.; Hojo, S.; Sekine, S.; Sawada, S.; Okumura, T.; Nagata, T.; Shimada, Y.; Tsukada, K. Expression of aquaporin-1 is a poor prognostic factor for stage II and III colon cancer. *Mol. Clin. Oncol.* **2013**, *1*, 953–958. [CrossRef]
57. Chae, Y.S.; Lee, S.J.; Lee, J.; Jung, J.H.; Park, H.Y. AQP3 expression predicts survival in patients with HER2-positive early breast cancer. *Cancer Res.* **2015**, *75*. [CrossRef]
58. Liu, S.; Zhang, S.; Jiang, H.; Yang, Y.; Jiang, Y. Co-expression of AQP3 and AQP5 in esophageal squamous cell carcinoma correlates with aggressive tumor progression and poor prognosis. *Med Oncol.* **2013**, *30*, 630. [CrossRef]
59. Peng, R.; Zhao, G.X.; Li, J.; Zhang, Y.; Shen, X.Z.; Wang, J.Y.; Sun, J.Y. Auphen and dibutyryl cAMP suppress growth of hepatocellular carcinoma by regulating expression of aquaporins 3 and 9 in vivo. *World J. Gastroenterol.* **2016**, *22*, 3341–3354. [CrossRef]
60. Rubenwolf, P.; Thomas, C.; Denzinger, S.; Hartmann, A.; Burger, M.; Georgopoulos, N.T.; Otto, W. Loss of AQP3 protein expression is associated with worse progression-free and cancer-specific survival in patients with muscle-invasive bladder cancer. *World J. Urol.* **2015**, *33*, 1959–1964. [CrossRef]
61. Herculano-Houzel, S. The human brain in numbers: A linearly scaled-up primate brain. *Front. Hum. Neurosci.* **2009**, *3*, 31. [CrossRef] [PubMed]
62. Amiry-Moghaddam, M.; Ottersen, O.P. The molecular basis of water transport in the brain. *Nat. Rev. Neurosci.* **2003**, *4*, 991–1001. [CrossRef] [PubMed]
63. Speake, T.; Whitwell, C.; Kajita, H.; Majid, A.; Brown, P.D. Mechanisms of CSF secretion by the choroid plexus. *Microsc. Res. Tech.* **2001**, *52*, 49–59. [CrossRef]
64. Boassa, D.; Stamer, W.D.; Yool, A.J. Ion channel function of aquaporin-1 natively expressed in choroid plexus. *J. Neurosci. Off. J. Soc. Neurosci.* **2006**, *26*, 7811–7819. [CrossRef] [PubMed]
65. Badaut, J.; Regli, L. Distribution and possible roles of aquaporin 9 in the brain. *Neuroscience* **2004**, *129*, 971–981. [CrossRef] [PubMed]
66. Saadoun, S.; Papadopoulos, M.C.; Davies, D.C.; Bell, B.A.; Krishna, S. Increased aquaporin 1 water channel expression in human brain tumours. *Br. J. Cancer* **2002**, *87*, 621–623. [CrossRef] [PubMed]
67. Oshio, K.; Binder, D.K.; Liang, Y.; Bollen, A.; Feuerstein, B.; Berger, M.S.; Manley, G.T. Expression of the aquaporin-1 water channel in human glial tumors. *Neurosurgery* **2005**, *56*, 375–380. [CrossRef] [PubMed]

68. El Hindy, N.; Bankfalvi, A.; Herring, A.; Adamzik, M.; Lambertz, N.; Zhu, Y.; Siffert, W.; Sure, U.; Sandalcioglu, I.E. Correlation of aquaporin-1 water channel protein expression with tumor angiogenesis in human astrocytoma. *Anticancer Res.* **2013**, *33*, 609–613.
69. Deb, P.; Pal, S.; Dutta, V.; Boruah, D.; Chandran, V.M.; Bhatoe, H.S. Correlation of expression pattern of aquaporin-1 in primary central nervous system tumors with tumor type, grade, proliferation, microvessel density, contrast-enhancement and perilesional edema. *J. Cancer Res. Ther.* **2012**, *8*, 571–577. [CrossRef]
70. Longatti, P.; Basaldella, L.; Orvieto, E.; Dei Tos, A.; Martinuzzi, A. Aquaporin(s) expression in choroid plexus tumours. *Pediatr. Neurosurg.* **2006**, *42*, 228–233. [CrossRef]
71. Endo, M.; Jain, R.K.; Witwer, B.; Brown, D. Water channel (aquaporin 1) expression and distribution in mammary carcinomas and glioblastomas. *Microvasc. Res.* **1999**, *58*, 89–98. [CrossRef] [PubMed]
72. Georges, J.; Samuelson, G.; Misra, A.; Joy, A.; Huang, Y.; McQuilkin, M.; Yoshihiro, A.; Carpenter, D.; Butler, L.; Feuerstein, B. Aquaporin-1 water transport and infiltration of glioblastoma multiforme. *Neuro-Oncology* **2011**, *13*, iii8–iii9. [CrossRef]
73. Liao, Z.Q.; Ye, M.; Yu, P.G.; Xiao, C.; Lin, F.Y. Glioma-Associated Oncogene Homolog1 (Gli1)-Aquaporin1 pathway promotes glioma cell metastasis. *BMB Rep.* **2016**, *49*, 394–399. [CrossRef] [PubMed]
74. Guan, Y.; Chen, J.; Zhan, Y.; Lu, H. Effects of dexamethasone on C6 cell proliferation, migration and invasion through the upregulation of AQP1. *Oncol. Lett.* **2018**, *15*, 7595–7602. [CrossRef]
75. Hayashi, Y.; Edwards, N.A.; Proescholdt, M.A.; Oldfield, E.H.; Merrill, M.J. Regulation and function of aquaporin-1 in glioma cells. *Neoplasia (New York N.Y.)* **2007**, *9*, 777–787. [CrossRef]
76. Chen, Y.; Tachibana, O.; Oda, M.; Xu, R.; Hamada, J.I.; Yamashita, J.; Hashimoto, N.; Takahashi, J.A. Increased expression of aquaporin 1 in human hemangioblastomas and its correlation with cyst formation. *J. Neuro-Oncol.* **2006**, *80*, 219–225. [CrossRef] [PubMed]
77. El Hindy, N.; Rump, K.; Lambertz, N.; Zhu, Y.; Frey, U.H.; Bankfalvi, A.; Siffert, W.; Sure, U.; Peters, J.; Adamzik, M.; et al. The functional Aquaporin 1 -783G/C-polymorphism is associated with survival in patients with glioblastoma multiforme. *J. Surg. Oncol.* **2013**, *108*, 492–498. [CrossRef]
78. Ewelt, C.; Ardon, H.; Suero, E.; Günes, D.; Wölfer, J.; Fischer, B.; Stummer, W. Aquaporin 1 and 4 in 5-ALA fluorescent tumor tissue. *Neuro-Oncology* **2012**, *14*, iii27–iii28. [CrossRef]
79. Isokpehi, R.D.; Wollenberg Valero, K.C.; Graham, B.E.; Pacurari, M.; Sims, J.N.; Udensi, U.K.; Ndebele, K. Secondary Data Analytics of Aquaporin Expression Levels in Glioblastoma Stem-Like Cells. *Cancer Inform.* **2015**, *14*, 95–103. [CrossRef] [PubMed]
80. Longatti, P.; Basaldella, L.; Orvieto, E.; Dei Tos, A.P.; Martinuzzi, A. Aquaporin 1 expression in cystic hemangioblastomas. *Neurosci. Lett.* **2006**, *392*, 178–180. [CrossRef] [PubMed]
81. McCoy, E.S.; Haas, B.R.; Sontheimer, H. Water permeability through aquaporin-4 is regulated by protein kinase C and becomes rate-limiting for glioma invasion. *Neuroscience* **2010**, *168*, 971–981. [CrossRef] [PubMed]
82. Noell, S.; Fallier-Becker, P.; Mack, A.F.; Hoffmeister, M.; Beschorner, R.; Ritz, R. Water channels aquaporin 4 and -1 expression in subependymoma depends on the localization of the tumors. *PLoS ONE* **2015**, *10*, e0131367. [CrossRef] [PubMed]
83. Rouzaire-Dubois, B.; Ouanounou, G.; O'Regan, S.; Dubois, J.M. Sodium-dependent activity of aquaporin-1 in rat glioma cells: A new mechanism of cell volume regulation. *Pflug. Arch.* **2009**, *457*, 1187–1198. [CrossRef] [PubMed]
84. Wang, D.; Owler, B.K. Expression of AQP1 and AQP4 in paediatric brain tumours. *J. Clin. Neurosci.* **2011**, *18*, 122–127. [CrossRef] [PubMed]
85. Saito, Y.; Furukawa, T.; Obata, T.; Saga, T. Molecular imaging of aquaglycero-aquaporins: Its potential for cancer characterization. *Biol. Pharm. Bull.* **2013**, *36*, 1292–1298. [CrossRef]
86. Aras, Y.; Erguven, M.; Aktas, E.; Yazihan, N.; Bilir, A. Antagonist activity of the antipsychotic drug lithium chloride and the antileukemic drug imatinib mesylate during glioblastoma treatment in vitro. *Neurol. Res.* **2016**, *38*, 766–774. [CrossRef] [PubMed]
87. Capoccia, E.; Cirillo, C.; Marchetto, A.; Tiberi, S.; Sawikr, Y.; Pesce, M.; D'Alessandro, A.; Scuderi, C.; Sarnelli, G.; Cuomo, R.; et al. S100B-p53 disengagement by pentamidine promotes apoptosis and inhibits cellular migration via aquaporin-4 and metalloproteinase-2 inhibition in C6 glioma cells. *Oncol. Lett.* **2015**, *9*, 2864–2870. [CrossRef]

88. Chen, Y.; Gao, F.; Jiang, R.; Liu, H.; Hou, J.; Yi, Y.; Kang, L.; Liu, X.; Li, Y.; Yang, M. Down-Regulation of AQP4 Expression via p38 MAPK Signaling in Temozolomide-Induced Glioma Cells Growth Inhibition and Invasion Impairment. *J. Cell. Biochem.* **2017**, *118*, 4905–4913. [CrossRef]
89. Ding, T.; Ma, Y.; Li, W.; Liu, X.; Ying, G.; Fu, L.; Gu, F. Role of aquaporin-4 in the regulation of migration and invasion of human glioma cells. *Int. J. Oncol.* **2011**, *38*, 1521–1531. [CrossRef] [PubMed]
90. Ding, T.; Zhou, Y.; Sun, K.; Jiang, W.; Li, W.; Liu, X.; Tian, C.; Li, Z.; Ying, G.; Fu, L.; et al. Knockdown a water channel protein, aquaporin-4, induced glioblastoma cell apoptosis. *PLoS ONE* **2013**, *8*, e66751. [CrossRef]
91. Dua, R.K.; Devi, B.I.; Yasha, T.C. Increased expression of Aquaporin-4 and its correlation with contrast enhancement and perilesional edema in brain tumors. *Br. J. Neurosurg.* **2010**, *24*, 454–459. [CrossRef] [PubMed]
92. Fallier-Becker, P.; Noell, S.; Tatagiba, M.; Ritz, R.; Woburg, H.; Wolburg-Buchholz, K. An allograft glioma model reveals the dependence of aquaporin-4 expression on the brain microenvironment. *GLIA* **2013**, *61*, S216. [CrossRef]
93. Hu, H.; Yao, H.T.; Zhang, W.P.; Zhang, L.; Ding, W.; Zhang, S.H.; Chen, Z.; Wei, E.Q. Increased expression of aquaporin-4 in human traumatic brain injury and brain tumors. *J. Zhejiang Univ. Sci. B* **2005**, *6*, 33–37. [CrossRef] [PubMed]
94. Lim, B.C.; Chae, J.H.; Kim, S.K.; Park, S.H.; Wang, K.C.; Lee, J.Y.; Phi, J.H. Aquaporin-4 autoimmunity masquerading as a brainstem tumor. *J. Neurosurg. Pediatrics* **2014**, *14*, 301–305. [CrossRef] [PubMed]
95. Mou, K.; Chen, M.; Mao, Q.; Wang, P.; Ni, R.; Xia, X.; Liu, Y. AQP-4 in peritumoral edematous tissue is correlated with the degree of glioma and with expression of VEGF and HIF-alpha. *J. Neuro-Oncol.* **2010**, *100*, 375–383. [CrossRef] [PubMed]
96. Noell, S.; Ritz, R.; Wolburg-Buchholz, K.; Wolburg, H.; Fallier-Becker, P. An allograft glioma model reveals the dependence of aquaporin-4 expression on the brain microenvironment. *PLoS ONE* **2012**, *7*, e36555. [CrossRef]
97. Noell, S.; Wolburg-Buchholz, K.; Mack, A.F.; Ritz, R.; Tatagiba, M.; Beschorner, R.; Wolburg, H.; Fallier-Becker, P. Dynamics of expression patterns of AQP4, dystroglycan, agrin and matrix metalloproteinases in human glioblastoma. *Cell Tissue Res.* **2012**, *347*, 429–441. [CrossRef]
98. Saadoun, S.; Papadopoulos, M.C.; Davies, D.C.; Krishna, S.; Bell, B.A. Aquaporin-4 expression is increased in oedematous human brain tumours. *J. Neurol. Neurosurg. Psychiatry* **2002**, *72*, 262–265. [CrossRef] [PubMed]
99. Xia, H.; Ye, J.; Bai, H.; Wang, C. Effects of cetuximab combined with celecoxib on apoptosis and KDR and AQP1 expression in lung cancer. *Chin. J. Lung Cancer* **2013**, *16*, 625–631. [CrossRef]
100. Schob, S.; Surov, A.; Wienke, A.; Meyer, H.J.; Spielmann, R.P.; Fiedler, E. Correlation Between Aquaporin 4 Expression and Different DWI Parameters in Grade I Meningioma. *Mol. Imaging Biol.* **2017**, *19*, 138–142. [CrossRef] [PubMed]
101. Warth, A.; Muley, T.; Meister, M.; Herpel, E.; Pathil, A.; Hoffmann, H.; Schnabel, P.A.; Bender, C.; Buness, A.; Schirmacher, P.; et al. Loss of aquaporin-4 expression and putative function in non-small cell lung cancer. *BMC Cancer* **2011**, *11*, 161. [CrossRef] [PubMed]
102. Xiong, W.; Ran, J.; Jiang, R.; Guo, P.; Shi, X.; Li, H.; Lv, X.; Li, J.; Chen, D. MiRNA-320a inhibits glioma cell invasion and migration by directly targeting aquaporin 4. *Oncol. Rep.* **2018**, *39*, 1939–1947. [CrossRef] [PubMed]
103. Yang, L.; Wang, X.; Zhen, S.; Zhang, S.; Kang, D.; Lin, Z. Aquaporin-4 upregulated expression in glioma tissue is a reaction to glioma-associated edema induced by vascular endothelial growth factor. *Oncol. Rep.* **2012**, *28*, 1633–1638. [CrossRef] [PubMed]
104. Yang, W.C.; Zhou, L.J.; Zhang, R.; Yue, Z.Y.; Dong, H.; Song, C.Y.; Qian, H.; Lu, S.J.; Chang, F.F. Effects of propofol and sevoflurane on aquaporin-4 and aquaporin-9 expression in patients performed gliomas resection. *Brain Res.* **2015**, *1622*, 1–6. [CrossRef] [PubMed]
105. Zhao, W.J.; Zhang, W.; Li, G.L.; Cui, Y.; Shi, Z.F.; Yuan, F. Differential expression of MMP-9 and AQP4 in human glioma samples. *Folia Neuropathol.* **2012**, *50*, 176–186.
106. Yang, J.; Zhang, J.N.; Chen, W.L.; Wang, G.S.; Mao, Q.; Li, S.Q.; Xiong, W.H.; Lin, Y.Y.; Ge, J.W.; Li, X.X.; et al. Effects of AQP5 gene silencing on proliferation, migration and apoptosis of human glioma cells through regulating EGFR/ERK/p38 MAPK signaling pathway. *Oncotarget* **2017**, *8*, 38444–38455. [CrossRef]
107. Zhu, S.J.; Wang, K.J.; Gan, S.W.; Xu, J.; Xu, S.Y.; Sun, S.Q. Expression of aquaporin8 in human astrocytomas: Correlation with pathologic grade. *Biochem. Biophys. Res. Commun.* **2013**, *440*, 173–177. [CrossRef]

108. Fossdal, G.; Vik-Mo, E.O.; Sandberg, C.; Varghese, M.; Kaarbo, M.; Telmo, E.; Langmoen, I.A.; Murrell, W. Aqp 9 and brain tumour stem cells. *ScientificWorldJournal* **2012**, *2012*, 915176. [CrossRef]
109. Jelen, S.; Parm Ulhøi, B.; Larsen, A.; Frøkiær, J.; Nielsen, S.; Rützler, M. AQP9 Expression in Glioblastoma Multiforme Tumors Is Limited to a Small Population of Astrocytic Cells and CD15+/CalB+ Leukocytes. *PLoS ONE* **2013**, *8*, e75764. [CrossRef]
110. Lv, Y.; Huang, Q.; Dai, W.; Jie, Y.; Yu, G.; Fan, X.; Wu, A.; Miao, Q. AQP9 promotes astrocytoma cell invasion and motility via the AKT pathway. *Oncol. Lett.* **2018**, *16*, 6059–6064. [CrossRef]
111. Warth, A.; Simon, P.; Capper, D.; Goeppert, B.; Tabatabai, G.; Herzog, H.; Dietz, K.; Stubenvoll, F.; Ajaaj, R.; Becker, R.; et al. Expression pattern of the water channel aquaporin-4 in human gliomas is associated with blood-brain barrier disturbance but not with patient survival. *J. Neurosci. Res.* **2007**, *85*, 1336–1346. [CrossRef] [PubMed]
112. Nico, B.; Ribatti, D. Role of aquaporins in cell migration and edema formation in human brain tumors. *Exp. Cell Res.* **2011**, *317*, 2391–2396. [CrossRef] [PubMed]
113. Betz, A.L.; Iannotti, F.; Hoff, J.T. Brain edema: A classification based on blood-brain barrier integrity. *Cerebrovasc. Brain Metab. Rev.* **1989**, *1*, 133–154.
114. Isoardo, G.; Morra, I.; Chiarle, G.; Audrito, V.; Deaglio, S.; Melcarne, A.; Junemann, C.; Naddeo, M.; Cogoni, M.; Valentini, M.C.; et al. Different aquaporin-4 expression in glioblastoma multiforme patients with and without seizures. *Mol. Med.* **2012**, *18*, 1147–1151. [CrossRef] [PubMed]
115. Lan, Y.L.; Wang, X.; Lou, J.C.; Ma, X.C.; Zhang, B. The potential roles of aquaporin 4 in malignant gliomas. *Oncotarget* **2017**, *8*, 32345–32355. [CrossRef] [PubMed]
116. Zhu, C.; Chen, Z.; Jiang, Z. Expression, distribution and role of aquaporin water channels in human and animal stomach and intestines. *Int. J. Mol. Sci.* **2016**, *17*, 1399. [CrossRef] [PubMed]
117. Mobasheri, A.; Airley, R.; Hewitt, S.M.; Marples, D. Heterogeneous expression of the aquaporin 1 (AQP1) water channel in tumors of the prostate, breast, ovary, colon and lung: A study using high density multiple human tumor tissue microarrays. *Int. J. Oncol.* **2005**, *26*, 1149–1158. [CrossRef]
118. Kang, B.W.; Kim, J.G.; Chae, Y.S.; Lee, S.J.; Sohn, S.K.; Moon, J.H.; Seo, J.; Yoon, G.S. AQP1 expression and survival in patients with colon cancer. *J. Clin. Oncol.* **2014**, *32*. [CrossRef]
119. Pei, J.V.; Kourghi, M.; De Ieso, M.L.; Campbell, E.M.; Dorward, H.S.; Hardingham, J.E.; Yool, A.J. Differential inhibition of water and ion channel activities of mammalian aquaporin-1 by two structurally related bacopaside compounds derived from the medicinal plant bacopa monnieri. *Mol. Pharmacol.* **2016**, *90*, 496–507. [CrossRef]
120. Dorward, H.S.; Du, A.; Bruhn, M.A.; Wrin, J.; Pei, J.V.; Evdokiou, A.; Price, T.J.; Yool, A.J.; Hardingham, J.E. Pharmacological blockade of aquaporin-1 water channel by AqB013 restricts migration and invasiveness of colon cancer cells and prevents endothelial tube formation in vitro. *J. Exp. Clin. Cancer Res.* **2016**, *35*, 36. [CrossRef]
121. Kourghi, M.; Pei, J.V.; De Ieso, M.L.; Flynn, G.; Yool, A.J. Bumetanide derivatives AqB007 and AqB011 selectively block the aquaporin-1 ion channel conductance and slow cancer cell migration. *Mol. Pharmacol.* **2016**, *89*, 133–140. [CrossRef] [PubMed]
122. Smith, E.; Palethorpe, H.M.; Tomita, Y.; Pei, J.V.; Townsend, A.R.; Price, T.J.; Young, J.P.; Yool, A.J.; Hardingham, J.E. The purified extract from the medicinal plant bacopa monnieri, bacopaside II, inhibits growth of colon cancer cells in vitro by inducing cell cycle arrest and apoptosis. *Cells* **2018**, *7*, 81. [CrossRef] [PubMed]
123. Yong, J. Aquaporin-1 activity of plasma membrane affects HT20 colon cancer cell migration. *IUBMB Life* **2009**, *61*, 1001–1009. [CrossRef]
124. Shan, T.; Cui, X.; Li, W.; Lin, W.; Li, Y. AQP5: A novel biomarker that predicts poor clinical outcome in colorectal cancer. *Oncol. Rep.* **2014**, *32*, 1564–1570. [CrossRef] [PubMed]
125. Shan, T.; Zheng, B.; Chen, X.; Wu, T.; Ji, E.L.; Bai, Y.H.; Wang, J.X.; Xiao, X.L. Expression of AQP5 in colorectal cancer and its relationship with clinical outcome. *J. Xi'an Jiaotong Univ. (Med. Sci.)* **2015**, *36*, 815–818 and 853. [CrossRef]
126. Kang, S.K.; Chae, Y.K.; Woo, J.; Kim, M.S.; Park, J.C.; Lee, J.; Soria, J.C.; Jang, S.J.; Sidransky, D.; Moon, C. Role of human aquaporin 5 in colorectal carcinogenesis. *Am. J. Pathol.* **2008**, *173*, 518–525. [CrossRef]

127. Shi, X.; Wu, S.; Yang, Y.; Tang, L.; Wang, Y.; Dong, J.; Lü, B.; Jiang, G.; Zhao, W. AQP5 silencing suppresses p38 MAPK signaling and improves drug resistance in colon cancer cells. *Tumor Biol.* **2014**, *35*, 7035–7045. [CrossRef]
128. Shi, X.; Wu, S.; Yang, Y.; Tang, L.; Lü, B. Silencing AQP-5 on proliferation, apoptosis and chemosensitivity of human colon cancer HT-29 cells. *Chin. J. Cancer Biother.* **2013**, *20*, 306–311. [CrossRef]
129. Li, A.; Lu, D.; Zhang, Y.; Li, J.; Fang, Y.; Li, F.; Sun, J. Critical role of aquaporin-3 in epidermal growth factor-induced migration of colorectal carcinoma cells and its clinical significance. *Oncol. Rep.* **2013**, *29*, 535–540. [CrossRef]
130. Kong, B.; Zhao, S.P. Inhibitory effects of lentivirus mediated RNA interference targeting human AQP1 gene on the proliferation of human colon carcinoma SW480 cells and the expression of VEGF. *Int. J. Clin. Exp. Med.* **2016**, *9*, 8999–9006.
131. Kang, B.W.; Kim, J.G.; Lee, S.J.; Chae, Y.S.; Jeong, J.Y.; Yoon, G.S.; Park, S.Y.; Kim, H.J.; Park, J.S.; Choi, G.S.; et al. Expression of aquaporin-1, aquaporin-3, and aquaporin-5 correlates with nodal metastasis in colon cancer. *Oncology* **2015**, *88*, 369–376. [CrossRef] [PubMed]
132. Chen, C.; Ma, T.; Zhang, C.; Zhang, H.; Bai, L.; Kong, L.; Luo, J. Down-regulation of aquaporin 5-mediated epithelial-mesenchymal transition and anti-metastatic effect by natural product Cairicoside E in colorectal cancer. *Mol. Carcinog.* **2017**, *56*, 2692–2705. [CrossRef] [PubMed]
133. Esghaei, M.; Ghaffari, H.; Rahimi Esboei, B.; Ebrahimi Tapeh, Z.; Bokharaei Salim, F.; Motevalian, M. Evaluation of Anticancer Activity of Camellia Sinensis in the Caco-2 Colorectal Cancer Cell Line. *Asian Pac. J. Cancer Prev.* **2018**, *19*, 1697–1701. [PubMed]
134. Li, Q.; Yang, T.; Li, D.; Ding, F.; Bai, G.; Wang, W.; Sun, H. Knockdown of aquaporin-5 sensitizes colorectal cancer cells to 5-fluorouracil via inhibition of the Wnt-beta-catenin signaling pathway. *Biochem. Cell Biol. = Biochim. Biol. Cell.* **2018**, *96*, 572–579. [CrossRef] [PubMed]
135. Shi, X.M.; Wu, S.C.; Tang, L.; Yang, Y.B.; Lü, B.N. Effect of AQP-5-siRNA on the apoptosis of colon cancer cell line HT-29 cells and investigation for its mechanism. *Chin. J. Cancer Prev. Treat.* **2015**, *22*, 349–353.
136. Wu, D.Q.; Yang, Z.F.; Wang, K.J.; Feng, X.Y.; Lv, Z.J.; Li, Y.; Jian, Z.X. AQP8 inhibits colorectal cancer growth and metastasis by down-regulating PI3K/AKT signaling and PCDH7 expression. *Am. J. Cancer Res.* **2018**, *8*, 266–279. [PubMed]
137. Dou, R.; Deng, Y.; Huang, L.; Fu, S.; Tan, S.; Wang, L.; Lian, L.; Fang, L.; Fan, X.; Jin, G.; et al. Multi-microarray identifies lower AQP9 expression in adjuvant chemotherapy nonresponders with stage III colorectal cancer. *Cancer Lett.* **2013**, *336*, 106–113. [CrossRef] [PubMed]
138. Huang, D.; Feng, X.; Liu, Y.; Deng, Y.; Chen, H.; Chen, D.; Fang, L.; Cai, Y.; Liu, H.; Wang, L.; et al. AQP9-induced cell cycle arrest is associated with RAS activation and improves chemotherapy treatment efficacy in colorectal cancer. *Cell Death Dis.* **2017**, *8*, e2894. [CrossRef]
139. Yang, Z.H.; Feng, X.Z.; Huang, D.D.; Deng, Y.H.; Chen, H.; Wang, J. Aquaporin-9 overexpression activates AKT signal pathway and enhances chemosensitivity in colorectal cancer. *Gastroenterology* **2015**, *148*, S357–S358. [CrossRef]
140. Imaizumi, H.; Ishibashi, K.; Takenoshita, S.; Ishida, H. Aquaporin 1 expression is associated with response to adjuvant chemotherapy in stage II and III colorectal cancer. *Oncol. Lett.* **2018**, *15*, 6450–6456. [CrossRef]
141. Zheng, M. Classification and Pathology of Lung Cancer. *Surg. Oncol. Clin. N. Am.* **2016**, *25*, 447–468. [CrossRef] [PubMed]
142. Shimasaki, M.; Machida, Y.; Takahara, Y.; Toga, H.; Ueda, Y. Relationship of aquaporin 1, 3 and 5 expression in lung cancer cells to cellular differentiation, invasive growth and metastasis potential. *Eur. Respir. J.* **2011**, *38*, 384.
143. Yun, S.; Sun, P.L.; Jin, Y.; Kim, H.; Park, E.; Park, S.Y.; Lee, K.; Lee, K.; Chung, J.H. Aquaporin 1 is an independent marker of poor prognosis in lung adenocarcinoma. *J. Pathol. Transl. Med.* **2016**, *50*, 251–257. [CrossRef] [PubMed]
144. Verkman, A. Role of aquaporins in lung liquid physiology. *Respir. Physiol. Neurobiol.* **2007**, *159*, 324–330. [CrossRef]
145. Hoque, M.O.; Soria, J.C.; Woo, J.; Lee, T.; Lee, J.; Jang, S.J.; Upadhyay, S.; Trink, B.; Monitto, C.; Desmaze, C.; et al. Aquaporin 1 is overexpressed in lung cancer and stimulates NIH-3T3 cell proliferation and anchorage-independent growth. *Am. J. Pathol.* **2006**, *168*, 1345–1353. [CrossRef] [PubMed]

146. Lopez-Campos, J.L.; Sanchez Silva, R.; Gomez Izquierdo, L.; Marquez, E.; Ortega Ruiz, F.; Cejudo, P.; Barrot Cortes, E.; Toledo Aral, J.J.; Echevarria, M. Overexpression of Aquaporin-1 in lung adenocarcinomas and pleural mesotheliomas. *Histol. Histopathol.* **2011**, *26*, 451–459. [CrossRef] [PubMed]
147. Cagini, L.; Balloni, S.; Ludovini, V.; Andolfi, M.; Matricardi, A.; Potenza, R.; Vannucci, J.; Siggillino, A.; Tofanetti, F.R.; Bellezza, G.; et al. Variations in gene expression of lung macromolecules after induction chemotherapy for lung cancer. *Eur. J. Cardio-Thorac. Surg.* **2017**, *52*, 1077–1082. [CrossRef] [PubMed]
148. Liu, Y.L.; Matsuzaki, T.; Nakazawa, T.; Murata, S.; Nakamura, N.; Kondo, T.; Iwashina, M.; Mochizuki, K.; Yamane, T.; Takata, K.; et al. Expression of aquaporin 3 (AQP3) in normal and neoplastic lung tissues. *Hum. Pathol.* **2007**, *38*, 171–178. [CrossRef]
149. Chae, Y.K.; Woo, J.; Kim, M.J.; Kang, S.K.; Kim, M.S.; Lee, J.; Lee, S.K.; Gong, G.; Kim, Y.H.; Soria, J.C.; et al. Expression of aquaporin 5 (AQP5) promotes tumor invasion in human non small cell lung cancer. *PLoS ONE* **2008**, *3*, e2162. [CrossRef]
150. Jo, Y.M.; Park, T.I.; Lee, H.Y.; Jeong, J.Y.; Lee, W.K. Prognostic Significance of Aquaporin 5 Expression in Non-small Cell Lung Cancer. *J. Pathol. Transl. Med.* **2016**, *50*, 122–128. [CrossRef]
151. Song, T.; Yang, H.; Ho, J.C.M.; Tang, S.C.W.; Sze, S.C.W.; Lao, L.; Wang, Y.; Zhang, K.Y. Expression of aquaporin 5 in primary carcinoma and lymph node metastatic carcinoma of non-small cell lung cancer. *Oncol. Lett.* **2015**, *9*, 2799–2804. [CrossRef] [PubMed]
152. Chen, Z.; Zhang, Z.; Gu, Y.; Bai, C. Impaired migration and cell volume regulation in aquaporin 5-deficient SPC-A1 cells. *Respir. Physiol. Neurobiol.* **2011**, *176*, 110–117. [CrossRef] [PubMed]
153. Guo, K.; Jin, F. NFAT5 promotes proliferation and migration of lung adenocarcinoma cells in part through regulating AQP5 expression. *Biochem. Biophys. Res. Commun.* **2015**, *465*, 644–649. [CrossRef] [PubMed]
154. Zhang, L.; Lu, J.; Zhou, H.; Du, Z.; Zhang, G. Silencing of aquaporin 5 inhibits the growth of A549 lung cancer cells in vitro and in vivo. *Int. J. Oncol.* **2018**, *52*, 1643–1650. [CrossRef]
155. Chen, J.; Bai, C.; Zhang, M.; Ren, Z.; Hu, J. Expression of aquaporins and its significance in human pulmonary adenocarcinoma cell line SPC-A-1. *Chin. J. Lung Cancer* **2004**, *7*, 199–201.
156. Li, X.J.; Xiang, Y.; Ma, B.; Qi, X.Q. Effects of acetazolamide combined with or without NaHCO3 on suppressing neoplasm growth, metastasis and aquaporin-1 (AQP1) protein expression. *Int. J. Mol. Sci.* **2007**, *8*, 229–240. [CrossRef]
157. Liu, Y.H.; Zhu, W.L. Effects of cetuximab combined with afatinib on the expression of KDR and AQP1 in lung cancer. *Genet. Mol. Res.* **2015**, *14*, 16652–16661. [CrossRef]
158. Ma, B.; Xiang, Y.; Li, T.; Yu, H.M.; Li, X.J. Inhibitory effect of topiramate on Lewis lung carcinoma metastasis and its relation with AQP1 water channel. *Acta Pharmacol. Sin.* **2004**, *25*, 54–60. [PubMed]
159. Arif, M.; Kitchen, P.; Conner, M.T.; Hill, E.J.; Nagel, D.; Bill, R.M.; Dunmore, S.J.; Armesilla, A.L.; Gross, S.; Carmichael, A.R.; et al. Downregulation of aquaporin 3 inhibits cellular proliferation, migration and invasion in the MDA-MB-231 breast cancer cell line. *Oncol. Lett.* **2018**, *16*, 713–720. [CrossRef]
160. Ben, Y.; Chen, J.; Zhu, R.; Gao, L.; Bai, C. Upregulation of AQP3 and AQP5 induced by dexamethasone and ambroxol in A549 cells. *Respir. Physiol. Neurobiol.* **2008**, *161*, 111–118. [CrossRef]
161. Hara-Chikuma, M.; Watanabe, S.; Satooka, H. Involvement of aquaporin-3 in epidermal growth factor receptor signaling via hydrogen peroxide transport in cancer cells. *Biochem. Biophys. Res. Commun.* **2016**, *471*, 603–609. [CrossRef] [PubMed]
162. Ishimoto, S.; Wada, K.; Usami, Y.; Tanaka, N.; Aikawa, T.; Okura, M.; Nakajima, A.; Kogo, M.; Kamisaki, Y. Differential expression of aquaporin 5 and aquaporin 3 in squamous cell carcinoma and adenoid cystic carcinoma. *Int. J. Oncol.* **2012**, *41*, 67–75. [CrossRef] [PubMed]
163. Li, B.; Jin, L.; Zhong, K.; Du, D. Correlation of aquaporin 3 expression with the clinicopathologic characteristics of non-small cell lung cancer. *Chin. J. Lung Cancer* **2012**, *15*, 404–408. [CrossRef]
164. Zhang, Z.; Chen, Z.; Song, Y.; Zhang, P.; Hu, J.; Bai, C. Expression of aquaporin 5 increases proliferation and metastasis potential of lung cancer. *J. Pathol.* **2010**, *221*, 210–220. [CrossRef] [PubMed]
165. Zhang, Z.Q.; Zhu, Z.X.; Bai, C.X.; Chen, Z.H. Aquaporin 5 expression increases mucin production in lung adenocarcinoma. *Oncol. Rep.* **2011**, *25*, 1645–1650. [CrossRef] [PubMed]
166. Miao, Z.F.; Chang, E.E.; Tsai, F.Y.; Yeh, S.C.; Wu, C.F.; Wu, K.Y.; Wang, C.J.; Tsou, T.C. Increased aquaglyceroporin 9 expression disrupts arsenic resistance in human lung cancer cells. *Toxicol. In Vitro* **2009**, *23*, 209–216. [CrossRef]

167. Evans, J.; Akhter, A.; Carbone, D.; Dikov, M.; Tchekneva, E. AQP11 as a novel factor of lung cancer cell resistance to cisplatin. *J. Thorac. Oncol.* **2017**, *12*, S985–S986. [CrossRef]
168. Sinn, H.-P.; Kreipe, H. A brief overview of the WHO classification of breast tumors. *Breast Care* **2013**, *8*, 149–154. [CrossRef] [PubMed]
169. Zou, L.B.; Shi, S.; Zhang, R.J.; Wang, T.T.; Tan, Y.J.; Zhang, D.; Fei, X.Y.; Ding, G.L.; Gao, Q.; Chen, C.; et al. Aquaporin-1 plays a crucial role in estrogen-induced tubulogenesis of vascular endothelial cells. *J. Clin. Endocrinol. Metab.* **2013**, *98*, E672–E682. [CrossRef] [PubMed]
170. Luo, L.; Yang, R.; Zhao, S.; Chen, Y.; Hong, S.; Wang, K.; Wang, T.; Cheng, J.; Zhang, T.; Chen, D. Decreased miR-320 expression is associated with breast cancer progression, cell migration, and invasiveness via targeting Aquaporin 1. *Acta Biochim. Biophys. Sin. (Shanghai)* **2018**, *50*, 473–480. [CrossRef] [PubMed]
171. Yin, T.; Yu, S.; Xiao, L.; Zhang, J.; Liu, C.; Lu, Y.; Liu, C. Correlation between the expression of aquaporin 1 and hypoxia-inducible factor 1 in breast cancer tissues. *J. Huazhong Univ. Sci. Technol. Med Sci.* **2008**, *28*, 346–348. [CrossRef] [PubMed]
172. Sekine, S.; Shimada, Y.; Nagata, T.; Moriyama, M.; Omura, T.; Watanabe, T.; Hori, R.; Yoshioka, I.; Okumura, T.; Sawada, S.; et al. Prognostic significance of aquaporins in human biliary tract carcinoma. *Oncol. Rep.* **2012**, *27*, 1741–1747. [CrossRef]
173. Cao, X.C.; Zhang, W.R.; Cao, W.F.; Liu, B.W.; Zhang, F.; Zhao, H.M.; Meng, R.; Zhang, L.; Niu, R.F.; Hao, X.S.; et al. Aquaporin3 is required for FGF-2-induced migration of human breast cancers. *PLoS ONE* **2013**, *8*, e56735. [CrossRef] [PubMed]
174. Huang, Y.T.; Zhou, J.; Shi, S.; Xu, H.Y.; Qu, F.; Zhang, D.; Chen, Y.D.; Yang, J.; Huang, H.F.; Sheng, J.Z. Identification of Estrogen Response Element in Aquaporin-3 Gene that Mediates Estrogen-induced Cell Migration and Invasion in Estrogen Receptor-positive Breast Cancer. *Sci. Rep.* **2015**, *5*, 12484. [CrossRef] [PubMed]
175. Satooka, H.; Hara-Chikuma, M. Aquaporin-3 controls breast cancer cell migration by regulating hydrogen peroxide transport and its downstream cell signaling. *Mol. Cell. Biol.* **2016**, *36*, 1206–1218. [CrossRef] [PubMed]
176. Lee, S.J.; Chae, Y.S.; Kim, J.G.; Kim, W.W.; Jung, J.H.; Park, H.Y.; Jeong, J.Y.; Park, J.Y.; Jung, H.J.; Kwon, T.H. AQP5 expression predicts survival in patients with early breast cancer. *Ann. Surg. Oncol.* **2014**, *21*, 375–383. [CrossRef] [PubMed]
177. Lee, S.J.; Kang, B.W.; Kim, J.G.; Jung, J.H.; Lee, J.; Kim, W.W.; Park, H.Y.; Jeong, J.H.; Jeong, J.Y.; Park, J.Y.; et al. AQP5 Variants Affect Tumoral Expression of AQP5 and Survival in Patients with Early Breast Cancer. *Oncology* **2017**, *92*, 153–160. [CrossRef]
178. Li, X.; Pei, B.; Wang, H.; Tang, C.; Zhu, W.; Jin, F. Effect of AQP-5 silencing by siRNA interference on chemosensitivity of breast cancer cells. *Oncotargets Ther.* **2018**, *11*, 3359–3368. [CrossRef]
179. Jia, B.; Li, H.; Cha, N.; Bao, W.; Zhao, R.; Sun, S. Inhibition of aquaporin 5 suppresses proliferation, migration, and invasion of breast cancer cells by modulating mapk signaling. *Acta Med. Mediterr.* **2018**, *34*, 1397–1403. [CrossRef]
180. Shi, Z.; Zhang, T.; Luo, L.; Zhao, H.; Cheng, J.; Xiang, J.; Zhao, C. Aquaporins in human breast cancer: Identification and involvement in carcinogenesis of breast cancer. *J. Surg. Oncol.* **2012**, *106*, 267–272. [CrossRef]
181. Zhang, T.; Lu, X.W.; Cheng, J.; Xiang, J.Y.; Chen, D.Z. Decreased miR-320 and increased AQP1 in patients with breast cancer and the clinical significance. *Int. J. Gynecol. Cancer* **2013**, *23*, 678.
182. Li, Y.B.; Sun, S.R.; Han, X.H. Down-regulation of AQP4 inhibits proliferation, migration and invasion of human breast cancer cells: (breast cancer/AQP4/siRNA/E-cadherin/ERK pathway). *Folia Biol. (Czech Republic)* **2016**, *62*, 131–137.
183. Jung, H.J.; Park, J.Y.; Jeon, H.S.; Kwon, T.H. Aquaporin-5: A marker protein for proliferation and migration of human breast cancer cells. *PLoS ONE* **2011**, *6*, e28492. [CrossRef] [PubMed]
184. Kasimir-Bauer, S.; Heubner, M.; Otterbach, F.; Kimmig, R.; Siffert, W.; Adamzik, M. Prognostic relevance of the AQP5 -1364C>A polymorphism in primary breast cancer. *Mol. Med. Rep.* **2009**, *2*, 645–650. [CrossRef]
185. Yang, J.; Shi, Y.; Cheng, Q.; Qian, Y. Protein and mRNA expression of aquaporin-1 in epithelial ovarian tumors and its clinic significance. *Zhonghua Fu Chan Ke Za Zhi* **2005**, *40*, 623–626. [PubMed]

186. Thoroddsen, A.; Dahm-Kähler, P.; Lind, A.K.; Weijdegård, B.; Lindenthal, B.; Müller, J.; Brännström, M. The water permeability channels aquaporins 1–4 are differentially expressed in granulosa and theca cells of the preovulatory follicle during precise stages of human ovulation. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 1021–1028. [CrossRef]
187. Yang, J.H.; Yan, C.X.; Chen, X.J.; Zhu, Y.S. Expression of aquaglyceroporins in epithelial ovarian tumours and their clinical significance. *J. Int. Med Res.* **2011**, *39*, 702–711. [CrossRef]
188. Chen, X.; Chen, W.; Ding, X.; Zheng, W.; Zhang, Q.; Yang, J. Effects of aquaporins on chemosensitivity to cisplatin in ovarian cancer cells. *Arch. Gynecol. Obstet.* **2014**, *290*, 525–532. [CrossRef]
189. Ji, C.; Cao, C.; Lu, S.; Kivlin, R.; Amaral, A.; Kouttab, N.; Yang, H.; Chu, W.; Bi, Z.; Di, W.; et al. Curcumin attenuates EGF-induced AQP3 up-regulation and cell migration in human ovarian cancer cells. *Cancer Chemother. Pharmacol.* **2008**, *62*, 857–865. [CrossRef]
190. Peng, R.; Zhang, Y.; Zhao, G.X.; Li, J.; Shen, X.Z.; Wang, J.Y.; Sun, J.Y. Differential regulation of the expression of aquaporins 3 and 9 by Auphen and dbcAMP in the SMMC-7721 hepatocellular carcinoma cell line. *Biotech. Histochem.* **2016**, *91*, 333–341. [CrossRef]
191. Rubenwolf, P.C.; Otto, W.; Denzinger, S.; Hofstadter, F.; Wieland, W.; Georgopoulos, N.T. Expression of aquaporin water channels in human urothelial carcinoma: Correlation of AQP3 expression with tumour grade and stage. *World J. Urol.* **2014**, *32*, 991–997. [CrossRef]
192. Abdelrahman, A.E.; Fathy, A.; Elsebai, E.A.; Nawar, N.; Etman, W.M. Prognostic impact of Apaf-1, Cyclin D1, and AQP-5 in serous ovarian carcinoma treated with the first-line chemotherapy. *Ann. Diagn. Pathol.* **2018**, *35*, 27–37. [CrossRef]
193. Yang, J.H.; Shi, Y.F.; Cheng, Q.; Deng, L. Expression and localization of aquaporin-5 in the epithelial ovarian tumors. *Gynecol. Oncol.* **2006**, *100*, 294–299. [CrossRef] [PubMed]
194. Chen, X.; Zhou, C.; Yan, C.; Ma, J.; Zheng, W. Hyperosmotic stress induces cisplatin sensitivity in ovarian cancer cells by stimulating aquaporin-5 expression. *Exp. Ther. Med.* **2015**, *10*, 2055–2062. [CrossRef]
195. Ma, J.; Zhou, C.; Yang, J.; Ding, X.; Zhu, Y.; Chen, X. Expression of AQP6 and AQP8 in epithelial ovarian tumor. *J. Mol. Histol.* **2016**, *47*, 129–134. [CrossRef] [PubMed]
196. Yang, J.H.; Shi, Y.F.; Chen, X.D.; Qi, W.J. The influence of aquaporin-1 and microvessel density on ovarian carcinogenesis and ascites formation. *Int. J. Gynecol. Cancer* **2006**, *16*, 400–405. [CrossRef] [PubMed]
197. Yang, J.H.; Yu, Y.Q.; Yan, C.X. Localisation and expression of aquaporin subtypes in epithelial ovarian tumours. *Histol. Histopathol.* **2011**, *26*, 1197–1205. [CrossRef] [PubMed]
198. Yang, C.; Lim, W.; Bae, H.; Song, G. Aquaporin 3 is regulated by estrogen in the chicken oviduct and is involved in progression of epithelial cell-derived ovarian carcinomas. *Domest. Anim. Endocrinol.* **2016**, *55*, 97–106. [CrossRef]
199. Yang, J.; Yan, C.; Zheng, W.; Chen, X. Proliferation inhibition of cisplatin and aquaporin 5 expression in human ovarian cancer cell CAOV3. *Arch. Gynecol. Obstet.* **2012**, *285*, 239–245. [CrossRef]
200. Chinigarzadeh, A.; Muniandy, S.; Salleh, N. Combinatorial effect of genistein and female sex-steroids on uterine fluid volume and secretion rate and aquaporin (AQP)-1, 2, 5, and 7 expression in the uterus in rats. *Enviromental Toxicol.* **2017**, *32*, 832–844. [CrossRef]
201. Choi, Y.S.; Park, J.H.; Yoon, J.K.; Yoon, J.S.; Kim, J.S.; Lee, J.H.; Yun, B.H.; Park, J.H.; Seo, S.K.; Cho, S.; et al. Potential roles of aquaporin 9 in the pathogenesis of endometriosis. *Mol. Hum. Reprod.* **2019**, *25*, 373–384. [CrossRef] [PubMed]
202. Cui, D.; Sui, L.; Han, X.; Zhang, M.; Guo, Z.; Chen, W.; Yu, X.; Sun, Q.; Dong, M.; Ma, T.; et al. Aquaporin-3 mediates ovarian steroid hormone-induced motility of endometrial epithelial cells. *Hum. Reprod. (Oxf. Engl.)* **2018**, *33*, 2060–2073. [CrossRef]
203. Ducza, E.; Csanyi, A.; Szoke, E.; Pohoczky, K.; Hajagos-Toth, J.; Kothencz, A.; Tiszai, Z.; Gaspar, R. Significance of transient receptor potential vanilloid 4 and aquaporin 5 co-expression in the rat uterus at term. *Heliyon* **2019**, *5*, e02697. [CrossRef] [PubMed]
204. Ferre-Dolcet, L.; Yeste, M.; Vendrell, M.; Rigau, T.; Rodriguez-Gil, J.E.; Del Alamo, M.M.R. Uterine and placental specific localization of AQP2 and AQP8 is related with changes of serum progesterone levels in pregnant queens. *Theriogenology* **2020**, *142*, 149–157. [CrossRef] [PubMed]
205. Jiang, X.X.; Fei, X.W.; Zhao, L.; Ye, X.L.; Xin, L.B.; Qu, Y.; Xu, K.H.; Wu, R.J.; Lin, J. Aquaporin 5 Plays a Role in Estrogen-Induced Ectopic Implantation of Endometrial Stromal Cells in Endometriosis. *PLoS ONE* **2015**, *10*, e0145290. [CrossRef] [PubMed]

206. Zhou, F.; Qian, Z.; Huang, L. Low-dose mifepristone increased angiogenesis in a manner involving AQP1. *Arch. Gynecol. Obstet.* **2019**, *299*, 579–584. [CrossRef] [PubMed]
207. Pan, H.; Sun, C.C.; Zhou, C.Y.; Huang, H.F. Expression of aquaporin-1 in normal, hyperplasic, and carcinomatous endometria. *Int. J. Gynecol. Obstet.* **2008**, *101*, 239–244. [CrossRef]
208. Zhang, X.; Chen, Y.; Dong, L.; Shi, B. Effect of selective inhibition of aquaporin 1 on chemotherapy sensitivity of J82 human bladder cancer cells. *Oncol. Lett.* **2018**, *15*, 3864–3869. [CrossRef]
209. Qiu, J.; Zhang, Y.; Chen, H.; Guo, Z. MicroRNA-488 inhibits proliferation, invasion and EMT in osteosarcoma cell lines by targeting aquaporin 3. *Int. J. Oncol.* **2018**, *53*, 1493–1504. [CrossRef]
210. Chen, R.; Lin, C.; Gulijiahan, A.; Lalai, S. Expression and significance of aquaporin 3(AQP 3) in cervical carcinogenesis. *Chin. J. Clin. Oncol.* **2012**, *39*, 145–148. [CrossRef]
211. Chen, R.; Shi, Y.; Amiduo, R.; Tuokan, T.; Suzuk, L. Expression and Prognostic value of aquaporin 1, 3 in cervical carcinoma in women of Uygur ethnicity from Xinjiang, China. *PLoS ONE* **2014**, *9*, e98576. [CrossRef] [PubMed]
212. Ming, L.; Ying, S.; Jian, Z.; Rong, W.; Ya, G. Expression and role of AQP1 in cervical squamous carcinoma and its precancerous lesions. *J. Med Coll. PLA* **2008**, *23*, 237–242. [CrossRef]
213. Shen, Q.; Lin, W.; Luo, H.; Zhao, C.; Cheng, H.; Jiang, W.; Zhu, X. Differential Expression of Aquaporins in Cervical Precursor Lesions and Invasive Cervical Cancer. *Reprod. Sci.* **2016**, *23*, 1551–1558. [CrossRef] [PubMed]
214. Shi, Y.H.; Chen, R.; Talafu, T.; Nijiati, R.; Lalai, S. Significance and expression of aquaporin 1, 3, 8 in cervical carcinoma in Xinjiang Uygur women of China. *Asian Pac. J. Cancer Prev.* **2012**, *13*, 1971–1975. [CrossRef] [PubMed]
215. Chen, Y.; Miller, C.; Mosher, R.; Zhao, X.; Deeds, J.; Morrissey, M.; Bryant, B.; Yang, D.; Meyer, R.; Cronin, F.; et al. Identification of cervical cancer markers by cDNA and tissue microarrays. *Cancer Res.* **2003**, *63*, 1927–1935. [PubMed]
216. Zhang, T.; Zhao, C.; Chen, D.; Zhou, Z. Overexpression of AQP5 in cervical cancer: Correlation with clinicopathological features and prognosis. *Med. Oncol.* **2012**, *29*, 1998–2004. [CrossRef] [PubMed]
217. Chang, H.; Shi, Y.; Tuokan, T.; Chen, R.; Wang, X. Expression of aquaporin 8 and phosphorylation of Erk1/2 in cervical epithelial carcinogenesis: Correlation with clinicopathological parameters. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 3928–3937.
218. Shi, Y.H.; Rehemu, N.; Ma, H.; Tuokan, T.; Chen, R.; Suzuke, L. Increased migration and local invasion potential of SiHa cervical cancer cells expressing Aquaporin 8. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 1825–1828. [CrossRef]
219. Shi, Y.H.; Tuokan, T.; Lin, C.; Chang, H. Aquaporin 8 involvement in human cervical cancer SiHa migration via the EGFR-Erk1/2 pathway. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 6391–6395. [CrossRef] [PubMed]
220. Zou, L.B.; Zhang, R.J.; Tan, Y.J.; Ding, G.L.; Shi, S.; Zhang, D.; He, R.H.; Liu, A.X.; Wang, T.T.; Leung, P.C.; et al. Identification of estrogen response element in the aquaporin-2 gene that mediates estrogen-induced cell migration and invasion in human endometrial carcinoma. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E1399–E1408. [CrossRef]
221. Sekine, S.; Shimada, Y.; Nagata, T.; Sawada, S.; Yoshioka, I.; Matsui, K.; Moriyama, M.; Omura, T.; Osawa, S.; Shibuya, K.; et al. Role of aquaporin-5 in gallbladder carcinoma. *Eur. Surg. Res.* **2014**, *51*, 108–117. [CrossRef] [PubMed]
222. Chen, J.; Wang, T.; Zhou, Y.C.; Gao, F.; Zhang, Z.H.; Xu, H.; Wang, S.L.; Shen, L.Z. Aquaporin 3 promotes epithelial-mesenchymal transition in gastric cancer. *J. Exp. Clin. Cancer Res.* **2014**, *33*. [CrossRef] [PubMed]
223. Chen, L.; Li, Z.; Zhang, Q.; Wei, S.; Li, B.; Zhang, X.; Zhang, L.; Li, Q.; Xu, H.; Xu, Z. Silencing of AQP3 induces apoptosis of gastric cancer cells via downregulation of glycerol intake and downstream inhibition of lipogenesis and autophagy. *OncoTargets Ther.* **2017**, *10*, 2791–2804. [CrossRef] [PubMed]
224. Dong, X.; Wang, Y.; Zhou, Y.; Wen, J.; Wang, S.; Shen, L. Aquaporin 3 facilitates chemoresistance in gastric cancer cells to cisplatin via autophagy. *Cell Death Discov.* **2016**, *2*, 16087. [CrossRef] [PubMed]
225. Huang, Y.; Zhu, Z.; Sun, M.; Wang, J.; Guo, R.; Shen, L.; Wu, W. Critical role of aquaporin-3 in the human epidermal growth factor-induced migration and proliferation in the human gastric adenocarcinoma cells. *Cancer Biol. Ther.* **2010**, *9*, 1000–1007. [CrossRef]

226. Jiang, B.; Li, Z.; Zhang, W.; Wang, H.; Zhi, X.; Feng, J.; Chen, Z.; Zhu, Y.; Yang, L.; Xu, H.; et al. miR-874 inhibits cell proliferation, migration and invasion through targeting aquaporin-3 in gastric cancer. *J. Gastroenterol.* **2014**, *49*, 1011–1025. [CrossRef]
227. Li, Z.; Li, B.; Zhang, L.; Chen, L.; Sun, G.; Zhang, Q.; Wang, J.; Zhi, X.; Wang, L.; Xu, Z.; et al. The proliferation impairment induced by AQP3 deficiency is the result of glycerol uptake and metabolism inhibition in gastric cancer cells. *Tumor Biol.* **2016**, *37*, 9169–9179. [CrossRef]
228. Huang, Y.H.; Zhou, X.Y.; Wang, H.M.; Xu, H.; Chen, J.; Lv, N.H. Aquaporin 5 promotes the proliferation and migration of human gastric carcinoma cells. *Tumor Biol.* **2013**, *34*, 1743–1751. [CrossRef]
229. Chae, Y.K.; Kang, S.K.; Kim, M.S.; Woo, J.; Lee, J.; Chang, S.; Kim, D.W.; Kim, M.; Park, S.; Kim, I.; et al. Human AQP5 plays a role in the progression of chronic myelogenous leukemia (CML). *PLoS ONE* **2008**, *3*, e2594. [CrossRef]
230. Prata, C.; Facchini, C.; Leoncini, E.; Lenzi, M.; Maraldi, T.; Angeloni, C.; Zambonin, L.; Hrelia, S.; Fiorentini, D. Sulforaphane modulates AQP8-linked redox signalling in leukemia cells. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 10. [CrossRef]
231. Bhattacharjee, H.; Carbrey, J.; Rosen, B.P.; Mukhopadhyay, R. Drug uptake and pharmacological modulation of drug sensitivity in leukemia by AQP9. *Biochem. Biophys. Res. Commun.* **2004**, *322*, 836–841. [CrossRef] [PubMed]
232. Chau, D.; Ng, K.; Chan, T.S.Y.; Cheng, Y.Y.; Fong, B.; Tam, S.; Kwong, Y.L.; Tse, E. Azacytidine sensitizes acute myeloid leukemia cells to arsenic trioxide by up-regulating the arsenic transporter aquaglyceroporin 9. *J. Hematol. Oncol.* **2015**, *8*, 46. [CrossRef] [PubMed]
233. Iriyama, N.; Yuan, B.; Yoshino, Y.; Hatta, Y.; Horikoshi, A.; Aizawa, S.; Takeuchi, J.; Toyoda, H. Aquaporin 9, a promising predictor for the cytocidal effects of arsenic trioxide in acute promyelocytic leukemia cell lines and primary blasts. *Oncol. Rep.* **2013**, *29*, 2362–2368. [CrossRef]
234. Leung, J.; Pang, A.; Yuen, W.H.; Kwong, Y.L.; Tse, E.W.C. Relationship of expression of aquaglyceroporin 9 with arsenic uptake and sensitivity in leukemia cells. *Blood* **2007**, *109*, 740–746. [CrossRef] [PubMed]
235. Mazal, P.R.; Susani, M.; Wrba, F.; Haitel, A. Diagnostic significance of aquaporin-1 in liver tumors. *Hum. Pathol.* **2005**, *36*, 1226–1231. [CrossRef]
236. Chen, G.; Shi, Y.; Liu, M.; Sun, J. CircHIPK3 regulates cell proliferation and migration by sponging miR-124 and regulating AQP3 expression in hepatocellular carcinoma. *Cell Death Dis.* **2018**, *9*, 175. [CrossRef]
237. Chen, X.F.; Li, C.F.; Lü, L.; Mei, Z.C. Expression and clinical significance of aquaglyceroporins in human hepatocellular carcinoma. *Mol. Med. Rep.* **2016**, *13*, 5283–5289. [CrossRef] [PubMed]
238. Guo, X.; Sun, T.; Yang, M.; Li, Z.; Li, Z.; Gao, Y. Prognostic value of combined aquaporin 3 and aquaporin 5 overexpression in hepatocellular carcinoma. *Biomed Res. Int.* **2013**, *2013*, 206525. [CrossRef] [PubMed]
239. He, Z.; Dong, W.; Hu, J.; Ren, X. AQP5 promotes hepatocellular carcinoma metastasis via NF-κB-regulated epithelial-mesenchymal transition. *Biochem. Biophys. Res. Commun.* **2017**, *490*, 343–348. [CrossRef]
240. Katsurahara, K.; Otsuji, E.; Okamoto, K.; Fujiwara, H.; Nakanishi, M.; Kubota, T.; Murayama, Y.; Morimura, R.; Konishi, H.; Arita, T.; et al. Anticancer effects of heat shock on liver cancer via autophagic degradation of aquaporin 5. *Cancer Sci.* **2018**, *109*, 953. [CrossRef]
241. Zhang, Z.; Han, Y.; Sun, G.; Liu, X.; Jia, X.; Yu, X. MicroRNA-325-3p inhibits cell proliferation and induces apoptosis in hepatitis B virus-related hepatocellular carcinoma by down-regulation of aquaporin 5. *Cell. Mol. Biol. Lett.* **2019**, *24*, 13. [CrossRef] [PubMed]
242. Li, C.F.; Zhang, W.G.; Liu, M.; Qiu, L.W.; Chen, X.F.; Lv, L.; Mei, Z.C. Aquaporin 9 inhibits hepatocellular carcinoma through up-regulating FOXO1 expression. *Oncotarget* **2016**, *7*, 44161–44170. [CrossRef] [PubMed]
243. Padma, S.; Smeltz, A.M.; Banks, P.M.; Iannitti, D.A.; McKillop, I.H. Altered aquaporin 9 expression and localization in human hepatocellular carcinoma. *HPB* **2009**, *11*, 66–74. [CrossRef]
244. Zhang, W.G.; Li, C.F.; Liu, M.; Chen, X.F.; Shuai, K.; Kong, X.; Lv, L.; Mei, Z.C. Aquaporin 9 is down-regulated in hepatocellular carcinoma and its over-expression suppresses hepatoma cell invasion through inhibiting epithelial-to-mesenchymal transition. *Cancer Lett.* **2016**, *378*, 111–119. [CrossRef]
245. Imrédi, E.; Liszkay, G.; Kenessey, I.; Plotár, V.; Gödény, M.; Tóth, B.; Fedorcsák, I.; Tímár, J. Aquaporin-1 Protein Expression of the Primary Tumor May Predict Cerebral Progression of Cutaneous Melanoma. *Pathol. Oncol. Res.* **2018**. [CrossRef] [PubMed]

246. Imrédi, E.; Tóth, B.; Doma, V.; Barbai, T.; Rásó, E.; Kenessey, I.; Tímár, J. Aquaporin 1 protein expression is associated with BRAF V600 mutation and adverse prognosis in cutaneous melanoma. *Melanoma Res.* **2016**, *26*, 254–260. [CrossRef]
247. Angelico, G.; Ieni, A.; Caltabiano, R.; Zeppa, P.; Tuccari, G. Aquaporin-1 expression in fluoro-edenite-induced mesothelioma effusions: An approach by cell-block procedure. *Cytopathology* **2018**, *29*, 455–460. [CrossRef]
248. Driml, J.; Griggs, K.; Cheng, Y.Y.; Reid, G.; Cheng, N.C.; Henderson, D.W.; Klebe, S. Effect of aquaporin 1 modulation in malignant pleural mesothelioma: Inhibition of cell proliferation and colony formation in vitro and tumour growth in vivo using a heterotopic mouse model. *J. Thorac. Oncol.* **2013**, *8*, S938–S939. [CrossRef]
249. Driml, J.; Pulford, E.; Moffat, D.; Karapetis, C.; Kao, S.; Griggs, K.; Henderson, D.W.; Klebe, S. Usefulness of aquaporin 1 as a prognostic marker in a prospective cohort of malignant mesotheliomas. *Int. J. Mol. Sci.* **2016**, *17*, 1041. [CrossRef]
250. Jagirdar, R.; Solenov, E.I.; Hatzoglou, C.; Molyvdas, P.A.; Gourgoulianis, K.I.; Zarogiannis, S.G. Gene expression profile of aquaporin 1 and associated interactors in malignant pleural mesothelioma. *Gene* **2013**, *517*, 99–105. [CrossRef]
251. Jagirdar, R.M.; Apostolidou, E.; Molyvdas, P.A.; Gourgoulianis, K.I.; Hatzoglou, C.; Zarogiannis, S.G. Influence of AQP1 on cell adhesion, migration, and tumor sphere formation in malignant pleural mesothelioma is substratum-and histological-type dependent. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2016**, *310*, L489–L495. [CrossRef] [PubMed]
252. Klebe, S.; Griggs, K.; Cheng, Y.; Driml, J.; Henderson, D.W.; Reid, G. Blockade of aquaporin 1 inhibits proliferation, motility, and metastatic potential of mesothelioma in vitro but not in an in vivo model. *Dis. Markers* **2015**, *2015*. [CrossRef] [PubMed]
253. Kon, T.; Ueno, T.; Suzuki, C.; Nunomura, J.; Igarashi, S.; Sato, T.; Tomiyama, M. Aquaporin-4 antibody positive neuromyelitis optica spectrum disorder associated with esophageal cancer. *J. Neuroimmunol.* **2017**, *309*, 38–40. [CrossRef] [PubMed]
254. Shimizu, H.; Shiozaki, A.; Ichikawa, D.; Fujiwara, H.; Konishi, H.; Ishii, H.; Komatsu, S.; Kubota, T.; Okamoto, K.; Kishimoto, M.; et al. The expression and role of Aquaporin 5 in esophageal squamous cell carcinoma. *J. Gastroenterol.* **2014**, *49*, 655–666. [CrossRef]
255. Chang, H.; Shi, Y.H.; Talaf, T.K.; Lin, C. Aquaporin-8 mediates human esophageal cancer Eca-109 cell migration via the EGFR-Erk1/2 pathway. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 7663–7671.
256. Zou, W.; Yang, Z.; Li, D.; Liu, Z.; Zou, Q.; Yuan, Y. AQP1 and AQP3 Expression are Associated with Severe Symptoms and Poor-prognosis of the Pancreatic Ductal Adenocarcinoma. *Appl. Immunohistochem. Mol. Morphol.* **2019**, *27*, 40–47. [CrossRef]
257. Huang, X.; Huang, L.; Shao, M. Aquaporin 3 facilitates tumor growth in pancreatic cancer by modulating mTOR signaling. *Biochem. Biophys. Res. Commun.* **2017**, *486*, 1097–1102. [CrossRef]
258. Hwang, I.; Jung, S.I.; Hwang, E.C.; Song, S.H.; Lee, H.S.; Kim, S.O.; Kang, T.W.; Kwon, D.; Park, K. Expression and localization of aquaporins in benign prostate hyperplasia and prostate cancer. *Chonnam Med. J.* **2012**, *48*, 174–178. [CrossRef]
259. Pan, X.Y.; Guo, H.; Han, J.; Hao, F.; An, Y.; Xu, Y.; Xiaokaiti, Y.; Pan, Y.; Li, X.J. Ginsenoside Rg3 attenuates cell migration via inhibition of aquaporin 1 expression in PC-3M prostate cancer cells. *Eur. J. Pharmacol.* **2012**, *683*, 27–34. [CrossRef]
260. Chen, J.; Wang, Z.; Xu, D.; Liu, Y.; Gao, Y. Aquaporin 3 promotes prostate cancer cell motility and invasion via extracellular signal-regulated kinase 1/2-mediated matrix metalloproteinase-3 secretion. *Mol. Med. Rep.* **2015**, *11*, 2882–2888. [CrossRef] [PubMed]
261. Chen, Q.; Zhu, L.; Zong, H.; Song, X.; Wang, L.; Wang, X.; Yang, D.; Wang, J. Subcellular localization of aquaporin 3 in prostate cancer is regulated by RalA. *Oncol. Rep.* **2018**, *39*, 2171–2177. [CrossRef] [PubMed]
262. Ismail, M.; Bokaee, S.; Davies, J.; Harrington, K.J.; Pandha, H. Inhibition of the aquaporin 3 water channel increases the sensitivity of prostate cancer cells to cryotherapy. *Br. J. Cancer* **2009**, *100*, 1889–1895. [CrossRef]
263. Li, J.; Wang, Z.; Chong, T.; Chen, H.; Li, H.; Li, G.; Zhai, X.; Li, Y. Over-expression of a poor prognostic marker in prostate cancer: AQP5 promotes cells growth and local invasion. *World J. Surg. Oncol.* **2014**, *12*. [CrossRef] [PubMed]
264. Huang, Y.; Murakami, T.; Sano, F.; Kondo, K.; Nakaigawa, N.; Kishida, T.; Kubota, Y.; Nagashima, Y.; Yao, M. Expression of Aquaporin 1 in Primary Renal Tumors: A Prognostic Indicator for Clear-Cell Renal Cell Carcinoma. *Eur. Urol.* **2009**, *56*, 690–699. [CrossRef] [PubMed]

265. Mobley, J.; Morrissey, J.; Bhayani, S.; Song, J.; Vetter, J.; Kharasch, E.; Figenshau, R. Urine aquaporin-1 and perilipin-2: Can these markers assist in the evaluation of small renal masses? *J. Endourol.* **2013**, *27*, A3. [CrossRef]
266. Morrissey, J.J.; Kharasch, E.D. The specificity of urinary aquaporin 1 and perilipin 2 to screen for renal cell carcinoma. *J. Urol.* **2013**, *189*, 1913–1920. [CrossRef] [PubMed]
267. Morrissey, J.J.; Mobley, J.; Figenshau, R.S.; Vetter, J.; Bhayani, S.; Kharasch, E.D. Urine aquaporin 1 and perilipin 2 differentiate renal carcinomas from other imaged renal masses and bladder and prostate cancer. *Mayo Clin. Proc.* **2015**, *90*, 35–42. [CrossRef] [PubMed]
268. Morrissey, J.J.; Mobley, J.; Song, J.; Vetter, J.; Luo, J.; Bhayani, S.; Figenshau, R.S.; Kharasch, E.D. Urinary concentrations of aquaporin-1 and perilipin-2 in patients with renal cell carcinoma correlate with tumor size and stage but not grade. *Urology* **2014**, *83*, 256.e9–256.e14. [CrossRef]
269. Rentsch, C.A.; Bachmann, A. Editorial Comment on: Expression of Aquaporin 1 in Primary Renal Tumors: A Prognostic Indicator of Clear-Cell Renal Cell Carcinoma. *Eur. Urol.* **2009**, *56*, 699. [CrossRef]
270. Sreedharan, S.; Petros, J.A.; Master, V.A.; Ogan, K.; Pattaras, J.G.; Roberts, D.L.; Lian, F.; Arnold, R.S. Aquaporin-1 protein levels elevated in fresh urine of renal cell carcinoma patients: Potential use for screening and classification of incidental renal lesions. *Dis. Markers* **2014**, *2014*, 6. [CrossRef]
271. Ticozzi-Valerio, D.; Raimondo, F.; Pitto, M.; Rocco, F.; Bosari, S.; Perego, R.; Sarto, C.; Di Fonzo, A.; Bosso, N.; Mocarelli, P.; et al. Differential expression of AQP1 in microdomain-enriched membranes of renal cell carcinoma. *Proteom. Clin. Appl.* **2007**, *1*, 588–597. [CrossRef] [PubMed]
272. Allory, Y.; Bazille, C.; Vieillefond, A.; Molinie, V.; Cochand-Priollet, B.; Cussenot, O.; Callard, P.; Sibony, M. Profiling and classification tree applied to renal epithelial tumours. *Histopathology* **2008**, *52*, 158–166. [CrossRef] [PubMed]
273. Nicchia, G.P.; Stigliano, C.; Sparaneo, A.; Rossi, A.; Frigeri, A.; Svelto, M. Inhibition of aquaporin-1 dependent angiogenesis impairs tumour growth in a mouse model of melanoma. *J. Mol. Med.* **2013**, *91*, 613–623. [CrossRef] [PubMed]
274. Pulford, E.; McEvoy, J.; Hocking, A.; Prabhakaran, S.; Griggs, K.; Klebe, S. The effect of aquaporin 1-inhibition on vasculogenic mimicry in malignant mesothelioma. *Int. J. Mol. Sci.* **2017**, *18*, 2293. [CrossRef] [PubMed]
275. Simone, L.; Gargano, C.D.; Pisani, F.; Cibelli, A.; Mola, M.G.; Frigeri, A.; Svelto, M.; Nicchia, G.P. Aquaporin-1 inhibition reduces metastatic formation in a mouse model of melanoma. *J. Cell. Mol. Med.* **2018**, *22*, 904–912. [CrossRef] [PubMed]
276. Vacca, A.; Frigeri, A.; Ribatti, D.; Nicchia, G.P.; Nico, B.; Ria, R.; Svelto, M.; Dammacco, F. Microvessel overexpression of aquaporin 1 parallels bone marrow angiogenesis in patients with active multiple myeloma. *Br. J. Haematol.* **2001**, *113*, 415–421. [CrossRef] [PubMed]
277. Hara-Chikuma, M.; Verkman, A.S. Prevention of skin tumorigenesis and impairment of epidermal cell proliferation by targeted aquaporin-3 gene disruption. *Mol. Cell. Biol.* **2008**, *28*, 326–332. [CrossRef]
278. Nakakoshi, M.; Morishita, Y.; Usui, K.; Ohtsuki, M.; Ishibashi, K. Identification of a keratinocarcinoma cell line expressing AQP3. *Biol. Cell* **2006**, *98*, 95–100. [CrossRef]
279. Seleit, I.; Bakry, O.A.; Al Sharaky, D.; Ragheb, E. Evaluation of Aquaporin-3 Role in Nonmelanoma Skin Cancer: An Immunohistochemical Study. *Ultrastruct. Pathol.* **2015**, *39*, 306–317. [CrossRef]
280. Matsuo, K.; Kawano, K. Immunohistochemical distribution and morphometric analysis of aquaporin-3 in oral squamous cell carcinoma. *Int. J. Oral Maxillofac. Surg.* **2014**, *43*, 13–21. [CrossRef]
281. Lehnerdt, G.F.; Bachmann, H.S.; Adamzik, M.; Panic, A.; Köksal, E.; Weller, P.; Lang, S.; Schmid, K.W.; Siffert, W.; Bankfalvi, A. AQP1, AQP5, Bcl-2 and p16 in pharyngeal squamous cell carcinoma. *J. Laryngol. Otol.* **2015**, *129*, 580–586. [CrossRef] [PubMed]
282. Niu, D.; Kondo, T.; Nakazawa, T.; Kawasaki, T.; Yamane, T.; Mochizuki, K.; Kato, Y.; Matsuzaki, T.; Takata, K.; Katoh, R. Differential expression of aquaporins and its diagnostic utility in thyroid cancer. *PLoS ONE* **2012**, *7*, e40770. [CrossRef] [PubMed]
283. Liu, J.; Zhang, W.Y.; Ding, D.G. Expression of aquaporin 1 in bladder uroepithelial cell carcinoma and its relevance to recurrence. *Asian Pac. J. Cancer Prev.* **2015**, *16*, 3973–3976. [CrossRef] [PubMed]
284. Breyer, J.; Otto, W.; Burger, M.; Hartmann, A.; Rubenwolf, P.C. Aquaporin 3 expression loss in urothelial carcinoma: Association with tumor invasion depth, but not with grading? *Bladder Cancer* **2017**, *3*, 31–34. [CrossRef] [PubMed]

285. Hachez, C.; Chaumont, F. Aquaporins: A family of highly regulated multifunctional channels. *Adv. Exp. Med. Biol.* **2010**, *679*, 1–17. [PubMed]
286. Ponten, F.; Jirstrom, K.; Uhlen, M. The Human Protein Atlas–a tool for pathology. *J. Pathol.* **2008**, *216*, 387–393. [CrossRef]
287. Uhlen, M.; Zhang, C.; Lee, S.; Sjostedt, E.; Fagerberg, L.; Bidkhori, G.; Benfeitas, R.; Arif, M.; Liu, Z.; Edfors, F.; et al. A pathology atlas of the human cancer transcriptome. *Science* **2017**, *357*. [CrossRef]