Review

Deniz Tuna Edizer*, Zeynep Akcali, Asım Leblebici, Sıla Övgü Korkut and Ender Ellidokuz

A dual role of proton pump inhibition on cancer: a critical review

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Abstract: Proton pump inhibitors (PPIs) are widely used to suppress gastric acid secretion. Proton pumps belong to the family of ATPase and among them P-ATPase and V-ATPase types regulate intracellular as well as extracellular acid equilibrium. The main aim of the current survey is to present the existing literature putting forth the relation between cancer with both the use of PPIs and proton pumps from positive and negative aspects. To perform an objective study, various types of proton pumps and their relation to cancer have been taken into account. Up to date, the studies have been considered in the time range from 2011 to 2021 via various databases (PubMed, Scopus, and Google Scholar). H^+/K^+ ATPase, located within the gastric parietal cells, is one of the most important examples of P-ATPases. The findings of the literature review along with criticism were presented as decreased P-ATPase expression can be used as a marker for gastric cancer diagnosis whereas the association of the proton pump with cancer may be mainly due to V-ATPase. In conclusion, molecular, epidemiological, and bioinformatic studies are required to enlighten the subject.

Keywords: cancer; carcinogenesis; proton pump inhibitors; proton pumps.

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***Corresponding author: Deniz Tuna Edizer**, MD, Assoc. Prof, MSc, Translational Oncology Department, Dokuz Eylul University, Oncology Institute, Izmir, Türkiye; and Ear Nose Throat Department, Acibadem University, Acibadem Atakent Hospital, Turgut Ozal Mah. No: 16, Kucukcekmece, Istanbul, Türkiye, Phone: +905335714289, E-mail: deniztunaedizer@yahoo.com. https://orcid.org/0000-0003-4448-1881
Zeynep Akcali, Translational Oncology Department, Dokuz Eylul University, Oncology Institute, Izmir, Türkiye; and Nephrology Department, Ege University, Izmir, Türkiye. https://orcid.org/0000-0003-4419-5164
Asım Leblebici, Translational Oncology Department, Dokuz Eylul University, Oncology Institute, Izmir, Türkiye. https://orcid.org/0000-0002-5197-6631
Sıla Övgü Korkut, Translational Oncology Department, Dokuz Eylul University, Oncology Institute, Izmir, Türkiye; and Faculty of Engineering and Architecture, Department of Engineering Sciences, Izmir Katip Celebi University, Izmir, Türkiye. https://orcid.org/0000-0003-4784-2013
Ender Ellidokuz, Translational Oncology Department, Dokuz Eylul University, Oncology Institute, Izmir, Türkiye; and Gastroenterolojgy Department, Dokuz Eylul University, Izmir, Türkiye. https://orcid.org/0000-0001-5863-3298

Introduction

Proton pump inhibitors (PPIs) are among the most commonly used drugs by beating histamine-2 receptor blockers because of their suppressive effects on gastric acid secretion and their use in gastroesophageal reflux disease (GERD), peptic ulcer, erosive esophagitis treatment.

Proton pumps are minor members of the ATPase family. P-ATPase and V-ATPase proton pumps, which are subgroups of the ATPase family, perform many functions by tuning the pH balance both inside and outside the cell.

This survey aims to evaluate the relationship of the two pump groups with cancer (facilitating or protecting cancer development) in light of the literature.

Effects of proton pumps

P-ATPase

H^+/K^+ ATPase, secreted from parietal cells, regulate the exchange of cytoplasmic H^+ with extracellular K^+. Hydrochloric acid (HCl) is formed by the combination of the H ion secreted into the gastric lumen with the luminal Cl ion. Tight regulation of parietal cells ensures proper secretion of HCl. Inhibition of H^+/K^+ ATPase is the most effective way for the prevention of gastric acid secretion [1].

V-ATPase

V-ATPases are ATP-dependent proton pumps that have a variety of functions including providing energy for

membrane transport processes and the regulation of acidity of the cells and organelles. Dysfunction of ATPase is seen in many diseases such as osteopetrosis and renal acidosis [2, 3].

V-ATPases play major roles in many physiological and pathophysiological conditions. V-ATPase generates an electrochemical gradient across the cell membranes and this gradient provides energy for cellular processes. Acidification of intracellular vesicles and organelles following activation of V-ATPase results in the formation of the necessary environment for many biological events.

The relationship between V-ATPase activity and carcinogenesis is well established. Increased activity of V-ATPase induces cancer invasiveness and metastasis, whereas the decreased activity of V-ATPase, e.g., following the use of V-ATPase inhibitors, inhibits cancer progression [4].

Tumor cells express V-ATPase which results in an acidic microenvironment and induces cancer growth and infiltration. The acidic tumor microenvironment is necessary for cancer progression and metastasis.

Lysosomal enzymes secreted by the tumor cells play a major role in the degradation of the extracellular matrix. These enzymes are more active at low pH. Acidification of the tumor microenvironment is provided by the V-ATPases. Low pH may cause extracellular matrix (ECM) degradation and remodel through the activation of proteolytic enzymes which contribute to invasion and cancer metastas.

V-ATPase inhibitors were classified as plecomacrolide antibiotics (concanamycin and bafilomycin), benzolactone enamides (salicylamide, apicularens, lobatamides, oximidines, cruentaren), archazolid, indoyls and late-generation V-ATPase inhibitors [5].

V-ATPase inhibition has also been shown to induce apoptosis in many tumor types through caspase-dependent and independent mechanisms [6].

Bafilomycin A1 and concanamycin A inhibit growth and induce apoptosis in different human cell lines. Bafilomycin A1 was assessed as a potential anticancer agent because it inhibits cell proliferation and tumor growth.

Specific VATPase inhibitors for mammals belonging to the benzolactone enamide class have also shown promise as anticancer agents. Proton secretion by the tumor cells leads to acidification of the extracellular medium and keeps the cytoplasm more alkaline. Acidic medium facilitates extracellular matrix (ECM) degradation through the activation of the proteolytic enzymes (especially matrix metalloproteinases) which is mandatory for cancer invasion as well as metastasis development. Studies with V-ATPase inhibitors had also revealed that these agents have the potential to suppress the incidence of metastasis development. Treatment with V-ATPase inhibitors lowers H+ extrusion, both *in vitro* and *in vivo* [5].

V-ATPase functions to increase lysosomal pH and impairs autophagy. On the other hand, V-ATPase inhibition induces autophagy and leads to the accumulation of autophagosomes [3, 6]. Carcinogenesis depends on autophagy, especially during development of metastasis. Autophagy is a conserved, self-degradation system that is critical for maintaining cellular homeostasis during stress conditions. Dysregulated autophagy has implications in both health and disease. Specifically, in cancer, autophagy plays a dichotomous role by inhibiting tumor initiation but supporting tumor progression. There is evidence that autophagy has reduced the effectiveness of chemotherapeutics [7]. V-ATPase has a similar effect on chemotherapeutics as well. Therefore, the use of V-ATPase inhibitors has an indirect effect on chemotherapeutic drug effectiveness [8].

V-ATPases have also a role in chemoresistance to antineoplastic agents and V-ATPase inhibitors may be used to manage drug resistance in cancer treatment. V-ATPase inhibition alters the acidity of the tumor microenvironment and increases the chemosensitivity of the cancer cells to antineoplastic agents. Specific V-ATPase inhibition has also the potential to decrease the toxicity to normal cells [9]. The solid tumor microenvironment is more acidic than normal tissue [10, 11] due to V-ATPase dysregulation [12]. More precisely, the dysregulation of V-ATPase causes to increase of the rate of uptaken glucose and, therefore, to accumulate the lactate. The described process, which is also known as Warburg Effect, is demonstrated schematically in Figure 1. This process also leads to aggresivity of the tumor cells for attempting survival [10, 13–16].

Effects of PPIs on cancer

This section provides the possible relations between the use of proton pump inhibitors and cancer. The key aspects of the relationship can be divided into positive and negative. Prior to presenting the literature, some clues from the databases have been given to make this study much more powerful and meaningful.

Correlation of proton pumps with cancer

There is no epidemiological and in-silico evidence yet to prove the theoretically demonstrated cancer-proton pump relationship in humans. In addition to the literature review on this subject, Figure 2 reveals the changes in expression of proton pumps in some cancer tissues and the relationship of these cancers with proton pumps. Although proton pump inhibition has been associated with cancer development in

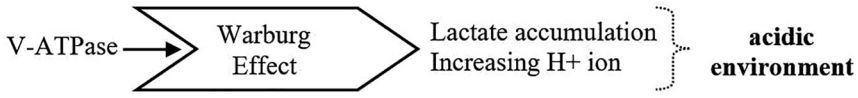

Figure 1: The basic scheme of the construction of acidic environment by the V-ATPase protein.

the literature, no evidence has yet been found in the large study for this critical review. Besides exemplifying remarkable literature, a further investigation has been done for discussing the relationship between the long-term use of PPIs and carcinogenesis. To do so, data extracted from the GEO database (The data covers normal and cancer tissues data sets as follows: GSE79973 for the stomach, GSE110224 for colon, GSE27651 for ovary, GSE18670 for the pancreas. The selected gene list consists of "ATP4A, ATP4B, ATP6V0A4, ATP6V1A, ATP6V1B1, ATP6V1B2, ATP6V1C1, ATP6V1C2, ATP6V1D, ATP6V1E1, ATP6V1E2, ATP6V1G1, ATP6V1V1G1, ATP6V1V1G1, ATP6V1V1G1") has been analyzed.

What is interesting in Figure 2 is the high positive correlation between ovarian cancer and the gene ATP6V1B1 which is a kind of subunit of V-ATPase whereas the other subunit of V-ATPase, ATP6V1H, has a high negative correlation with ovarian cancer. Moreover, it can be also observed from Figure 2 that ATP4A and ATP4B are significantly down regulated in gastic cancer. As highlighted previously, due to the high correlation of some subunits of V-ATPases/P-ATPases with some types of cancers, the use of PPIs can be a therapeutic strategy. Furthermore, it is seen in Figure 2 that P-ATPase mRNA expression is lesser in gastric cancer compared to normal gastric tissue [17]. These findings suggest that decreased P-ATPase expression can be used as a marker in the diagnosis of gastric cancer. Similar reductions were observed in pancreatic, colorectal, and ovarian cancers, but they were not statistically significant. On the other hand, since the expression of V-ATPase subunits is not statistically significant in gastric cancer, they have not considered markers for diagnosis. It is predicted that it may be more enlightening to plan studies in which other omics technologies will be used instead of only genomic and transcriptomic studies.

The positive effect of the use of PPIs: "the relation with the tumor microenvironment"

By the consensus of the authors V-ATPase and cancer-related publications have been focused on. To enrich a deep understanding of cancer disease, research on the tumor microenvironment has become popular in recent years [18–24]. The main aim of the current section is to present the literature knowledge on the relationship of proton pump inhibitors (PPI) on the tumor microenvironment.

A general search was conducted on two databases (Scopus and PubMed) to review relevant articles published until December 31, 2021. To do so, the algorithmic query has been developed as follows: ("tumor microenvironment" or "cancer") and ("V-ATPase" or "vacuolar H^+ ATPase" or "H^+ ATPase" or " H^+/K^+ ATPase " or "ATP4A" or "ATP4B"). With the help of the developed query all possible combinations coupling with tumor microenvironment/cancer and one of the ATPase proteins have been searched.

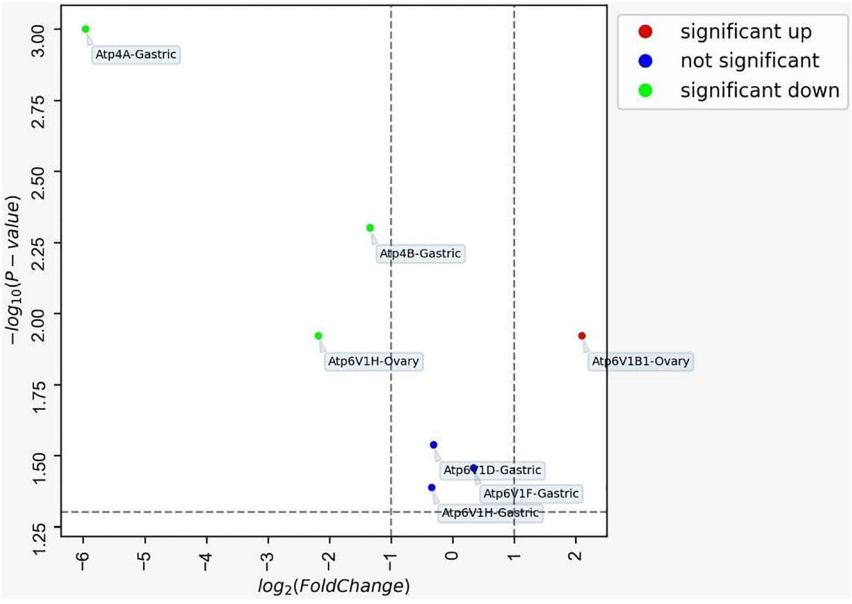

Figure 2: Correlation of cancer with P-ATPase and V-ATPase. We selected datasets containing gene expression data generated in normal and cancer tissues from the GEO database. Datasets GSE79973 for stomach, GSE110224 for colon, GSE27651 for ovary, and GSE18670 for pancreas were used. We found that "ATP4A, ATP4B, ATP6V1B1, ATP6V1D, ATP6V1F, ATP6V1H" genes showed statistically significant changes. Fold change, FDR-corrected p-value was calculated for target genes between normal and cancer tissues.

After data is extracted from the databases, Pandas libraries in Python language has been used as a tool for data preprocessing. Duplication of articles has been checked on the 'doi' of the articles. Thus, the articles whose doi number are no accessible are removed. All above-mentioned instructions have been implemented, 524 studies were recorded. A further exclusion has been done to preserve the consistency of the study. Due to the fact that the nature of the use of PPIs is to neutralize of the acidity of the medium, we have focused on the studies which contain at least one of the following keys: "Proton Pump", "Acidity", "vacuolar ATPase" "vacuolar H^+ ATPase", "V-ATPase", "proton pump inhibitor" (all case sensitivies has been taken into account). By doing so, the recorded articles have been reduced to 177 studies. Finally, the remaining 177 articles have been reduced to 33 articles by making an abstract review by the authors. Figure 3 illustrates the flow diagram of the review.

According the present review, the sample studies revealing the relationship between V-ATPase proton pump and cancer are as follows: V-ATPase is overexpressed in non-small cell lung cancer, and drug resistance of this cancer type is probably related to V-ATPase overexpression [25]. Kulshrestha et al. referred to the team's previous work, which inferred that the V-ATPase a2 isoform is overexpressed in cisplatin-resistant cells of ovarian cancer cells, targeting V-ATPase-V0a2 makes chemoresistance-resistant ovarian cancer cells susceptible to cisplatin treatment [26]. Moreover, there has not been a demonstrated correlational relationship between clinical drug resistance and V-ATPase expression [26]. In a study, which is mainly on ovarian cancer, that PPI could be, hopefully, a promising strategy to increase the efficacy of therapy in anti-epithelial ovarian carcinoma, despite drug resistance developed by vacuolar H + -ATPase overexpression [27]. Additionally, various studies have reported that V-ATPase expression is associated with glioma aggressiveness [28–30]. The authors have examined the proton pump expression of V-ATPase in gliomas. In that research paper, the authors have tested their in-silico findings on a small cohort of related brain tumors. Additionally, V-ATPase G1 (ATP6V1G1) expression is very high in glioblastomas and this expression is highly correlated to short-term rental survival [30]. Therefore, it was pointed out that inhibition of V-ATPase would be a new therapeutic approach for glioblastoma [31]. In addition to the aforementioned cancer types, it has been stated that the V-ATPase proton pump increases the invasive nature of the cancers such as pancreatic, breast, and esophagus [15, 32–35]. Furthermore, in colorectal cancer, it has been highlighted that ATP6L, which is a subunit of V-ATPase, triggers metastasis and is a potential target in tumor therapy [36].

Although there are various studies in the literature that long-term use of PPIs may pose a cancer risk [37–41], to the best knowledge of the authors there is no clear evidence yet. Nevertheless, a remarkable study conducted by Luciani et al. shows that PPIs (Omeprazole, esomeprazole, and pantoprazole) have proven through *in vitro* experiments that pretreatment with antitumor drugs can reduce acidification around the tumor [42]. The study has also demonstrated *in vivo* experiments that omeprazole can induce sensitivity to oral pretreatment cisplatin. In addition to the mentioned study, more recent studies have provided

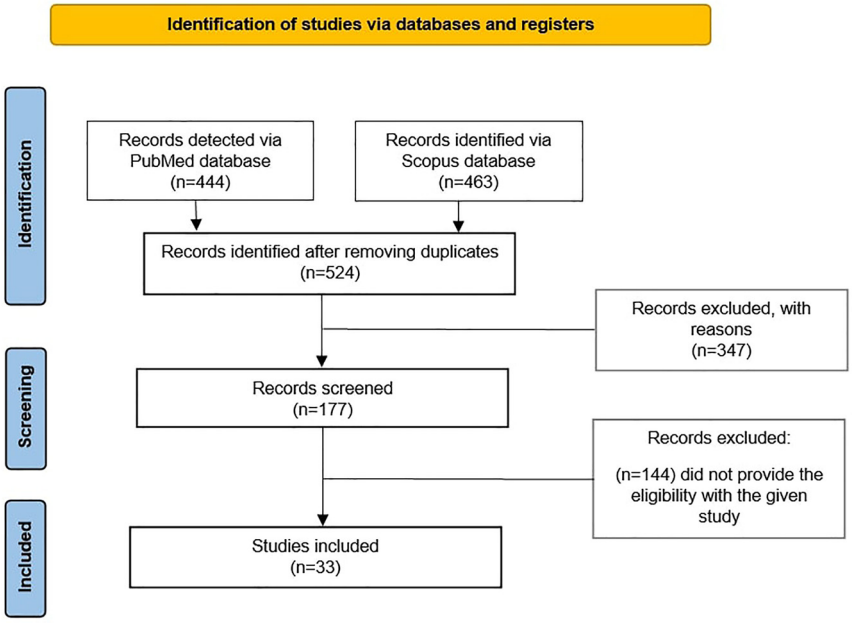

Figure 3: Flow diagram for selection of studies.

evidence that V-ATPase/H^+/K^+ ATPase pump inhibitors will contribute to the therapeutic strategy and increase chemosensitivity [10, 14, 34, 43, 44].

The negative effect of the use of PPIs: "long-term PPI" use on pre-cancerous lesions

Hypergastrinemia develops in response to deep acid-suppressing therapy. Hyperplasia of ECL cells may occur with prolonged hypergastrinemia, especially in individuals with *H. pylori* infection or more markedly increased gastrin levels [43]. It has been reported that ECL-like cell hyperplasia can lead to dysplasia and eventually into gastric carcinoid formation in both rats and humans [44]. Scarpignato et al. reported that two individuals using PPIs for more than 10 years developed well-differentiated neuroendocrine tumors [45]. However, other long-term studies of people using PPIs have not shown an increased risk of carcinoids [46]. Based on a systematic review by meta-analysis, long-term use of PPIs (≥12 months) was associated with an increased risk of fundic gastric metaplasia [47]. In animal models, the carcinogenicity of PPIs has been widely studied, particularly in rodents where PPIs cause cancer and other rare gastrointestinal (GI) tumors, whereas in humans this association is less clear. However, there is great concern with the long-term use of PPIs and the development of GI cancers, particularly gastric, colon cancer and carcinoid tumor.

It was concluded that PPI therapy is one of the strongest risk factors for the development of fundic gastric polyps (FGPs), and their high prevalence is probably due to increased prescription in recent years, but no evidence of dysplasia or sporadic cancer was observed. Evidence of malignant transformation was not found by Genta et al. using data from more than 6,000 FGP patients. Therefore, the evolution of FGPs towards dysplasia appears to be an extremely rare event and endoscopic follow-up for these polyps is not currently recommended [48].

In addition to being a well-known risk factor for gastric cancer, *H. pylori* infection is known to cause loss of parietal cells and thus decreased gastric secretion. The resulting hypochlorhydria may increase the risk of bacterial overgrowth responsible for worsening gastritis observed in *H. pylori*-infected patients treated with PPIs. Moreover, gastric atrophy and hypochlorhydria can lead to non-helicobacter microbiota overgrowth, which may increase the risk of gastric cancer in patients infected with *H. pylori* [49]. A subgroup analysis by Tran-Duy and coworkers added information about the duration of PPI therapy, reporting that after long-term treatment with PPI (>36 months), the interaction between *H. pylori* infection and PPI use may cause more disease. Compared to shorter treatment times, severe gastritis results in an increased risk of atrophic gastritis [47].

Another area of major concern is the effect of long-term PPI therapy and associated hypergastrinemia on ECL cells and the possible development of preneoplastic and carcinoid lesions. Similarly, Lundell and colleagues noted that long-term use of PPIs was associated with only moderate hypergastrinemia resulting in an increased prevalence of ECL cell hyperplasia, however, none of the patients included in the study developed a neuroendocrine tumor (NET) [50]. Neuroendocrine tumor development in patients using long-term therapy with PPI is an uncertain and rare event and therefore these findings may be incidental. Progression to dysplasia has only been reported in rare cases of Zollinger-Ellison syndrome and multiple endocrine neoplasia type I, but this is due to the presence of marked hypergastrinemia and chronic atrophic gastritis rather than PPI therapy.

Increased gastrin level, as a result of PPI inhibition, has been found to play a role in tumorigenesis in the GI tract, and high gastrin levels have also been shown to have a trophic effect on colon cancer cells *in vitro*. Therefore, theoretically, hypergastrinemia may lead to the development of colonic adenoma and colorectal cancer.

Results and conclusions

In the presented study, a comparative literature review has been conducted based on the focused question: Does the use of proton pump inhibitors associated with cancer? Besides the literature review, the study has been supported by data demonstrating the correlations between the use of PPIs and cancer.

It can be concluded that V-type ATPases accelerate the acidity of the tumor microenvironment and lead to a more aggressive nature of tumor cells that adapt to this environment. On one hand, existing evidence indicated that the use of PPIs (Omeprazole, esomeprazole and pantoprazole) decrease the acidic character of the tumor microenvironment and accentuate the effectiveness of cancer treatment. On the other hand, there are also remarkable studies underlining the long-term use of PPIs that might be associated with the development of metaplasia in the gastric corpus mucosa secondary to parietal cell loss and a causative factor for carcinoid tumors. According to the reported studies and findings, the use of PPIs and their association with cancer development has not been clarified yet. However, the use of PPIs can contribute to the therapeutic strategy of cancer and increase chemosensitivity.

P-ATPase mRNA expression is decreased in gastric cancer tissues than the healthy gastric tissue. Decreased

P-ATPase expression could be used as a candidate marker for gastric cancer diagnosis. The association between the proton pump with cancer might be mainly due to V-ATPase. It is crucial to note that additional molecular, epidemiological and bioinformatic studies are needed to understand the effects of the use of PPIs on cell selectivity and toxicity.

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