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Angiotensin-converting enzyme inhibitors for ovarian cancer? — a new adjuvant option or a silent trap

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Abstract

Background: Ovarian cancer is a huge therapeutic and financial problem for which approved treatments have already achieved their limit of efficiency. A cost-effective strategy to extend therapeutic options in this malignancy is drug repurposing aimed at overcoming chemoresistance. Here, angiotensin-converting enzyme inhibitors (ACE-I) are worth considering.

Material and methods: We searched literature for publications supporting the idea of adjuvant application of ACE-Is in ovarian malignancy. Then, we searched The Cancer Genome Atlas databases for relevant alternations of gene expression patterns. We also performed in silico structure-activity relationship evaluation for predicting ACE-Is'

cytotoxicity against ovarian cancer cell lines. Finally, we reviewed the potential obstacles in ACE-Is repurposing process.

Results: The alternation of angiotensin receptor expression in ovarian cancer translates into poorer patient survival. This confirms the participation of the renin-angiotensin system in ovarian carcinogenesis. In observational studies, ACE-Is were shown synergize with both, platinum-based chemotherapy as well as with antiangiogenic therapy. Consistently, our in silico simulation showed that ACE-Is are probably cytotoxic against ovarian cancer cells. However, the publications on their chemopreventive properties were inconclusive. In addition, some reports correlated ACE-Is use with increased general cancer incidence. We hypothesized that this effect could be associated with mutagenic nitrosamine formation in ACE-Is' pharmaceutical formulations, as was the case with angiotensin receptor blockers (ARBs) and other well-established pharmaceuticals.

Conclusions: Available data warrant further research into repositioning ACE-Is to ovarian cancer as chemosensitizers. Prior to this, however, a special research program is needed to detect possible genotoxic contaminants of ACE-Is.

Key words: repurposing; genotoxic impurities; chemoresistance; renin–angiotensin system

Introduction

Ovarian cancer is a major health problem that generates significant social burden globally in terms of epidemiology and economics. Among other cancers, it poses a huge diagnostic and therapeutic challenge, with strikingly high mortality rates. In Poland the number of deaths from ovarian cancer reached 3,000 in 2017, ranking it the fifth leading cause of mortality among all cancers, and the first among gynaecological cancers. These unfavourable statistics exist despite low incidence and prevalence rates [1]. Moreover, as per World Ovarian Cancer Coalition, future mortality prediction is pessimistic, with incidence set to rise by 47% by 2040. This prognosis regards particularly low- and middle-income countries [2]. Is is due to the expected increase in the women population over 60 years of age, i.e. those at the highest risk [1, 3]. Clinically, high mortality from ovarian cancer is caused by its asymptomatic development at early stages, late onset of clinical symptoms and lack of proper cost-effective screening techniques, leading to delayed diagnosis. In fact, 75% of patients are diagnosed at advanced III/IV clinical stage. The average 5-year overall survival (OS) is poor. It equals 44%, while in advanced stage it falls below 30%, making it one of the deadliest malignancies [1, 4, 5]. Besides, ovarian cancer is also difficult to treat. Its immunosuppressive nature and molecular targets deficiency limit the opportunities for personalised therapy or

immunotherapy [5, 6]. Consequently, the approved therapeutic options are scarce and they mainly involve the combination of surgery and platinum/taxanes-based chemotherapy. Other available chemotherapeutics, including gemcitabine, liposomal doxorubicin and topotecan, are less effective. The only modern drugs in ovarian cancer are bevacizumab and poly adenosine diphosphate-ribose polymerases (PARP) inhibitors. Bevacizumab is an anti-angiogenic agent [anti-vascular endothelial growth factor (VEGF) monoclonal antibody] used only in a selected group of patients in combination with platinum and taxanes. PARP inhibitors, in turn, are administered as maintenance therapy following completion of platinum-based treatment. Although they improve progression-free survival (PFS), their success is only modest, while their high cost and restricted reimbursement indications limit their accessibility [5]. Radiation therapy, in turn, is of marginal importance [7] as opposed to other gynaecological malignancies [8–10]. As a consequence, the management of ovarian cancer has been continuously dominated by traditional chemotherapy with the response rate to first-line treatment reaching 70–80%. However, 80% of women with advanced disease will relapse. In those patients the disease is incurable and it will require subsequent lines of chemotherapy, with gradually decreasing platinum-free interval and increasing platinum resistance. Resistance to first-line chemotherapy occurs in approximately 25% of cases and it is a serious clinical problem [11]. In fact, in this setting therapeutic options are extremely limited and provide no realistic chance of long-term remission. Ovarian cancer chemotherapy is also a huge, and still-increasing, financial burden, owing to increasing disease incidence and treatment toxicity. Polish National Health Fund Agency reported that in 2017 the direct financial burden of the management of 12,000 ovarian cancer patients accounted for PLN 231 million. Moreover, indirect costs and loss of potential revenue exceeded PLN 710 million. A substantial proportion of these figures involved the cost of chemotherapy and its side effects management. It means that with respect of public finances, more efficient and less toxic drugs are of extreme necessity [1].

An interesting strategy in developing new, cost-effective therapeutic solutions in ovarian cancer focuses on taxane- and platinum-sensitizing agents. Its idea is that enhancing cytotoxicity and reducing doses of cytotoxic drugs would decrease treatment resistance and mitigate side effects. At present, this approach also seems to represent the most optimal and viable opportunity for clinical intervention. Nevertheless, the difficulty in finding effective chemosensitizer in ovarian cancer stems from the fact that the underlying mechanisms of chemoresistance are extremely complex. They were demonstrated and discussed in Figure 1 [12, 13].

Thus, although a number of drug-candidates has been tested so far, none of them has been introduced into clinics [14–16]. Still, it is believed that finding an agent which targets a key resistance pathway and enhances cell response to the platinum-based treatments, would finally provide a long-anticipated therapeutic success in patients with poor prognosis. In this context, one approach of obtaining chemosensitizing compounds in ovarian cancer could be screening and repurposing of off-patent drugs which are already available in the pharmaceutical sector. This method is an alternative to *de novo* drug design, and it was mostly appreciated by the European Medicines Agency and the Food and Drug Administration during COVID-19 pandemic. Repurposing is also cheaper and faster than traditional drug discovery, since the existing preclinical and clinical knowledge on approved compounds allows skipping early drug development stages. As a result, the duration of clinical research can be reduced by 5–7 years. This also translates into a relatively high success rate of repurposed drugs, estimated at 30%, as opposed to 10% for innovative medicines. In addition, repurposed drugs are frequently relatively inexpensive and widely accessible. Hence, their timely and affordable access for patients with unmet medical need is possible [17–19]. With all these in mind, we previously conducted an extensive literature review and found a group of drug candidates with a clear opportunity for being repurposed to oncology. They were angiotensin converting-enzyme inhibitors (ACE-Is) which modulate the renin–angiotensin system (RAS) [20, 21]. Our previous reviews, however, did not cover the aspects of gynaecological malignancies. They also did not discuss the issues on potential detrimental activity of ACE-Is. Therefore, current review is an update of the pre-existing report, focused specifically on the significance of ACE-Is in ovarian cancer and potential opportunities for their re-profiling to become dedicated adjuvant therapies in this disease. Here, we have also highlighted the recently reported obstacles that may be important for the further development of this group of drugs.

Materials and methods

First, in order to find the justification for a more detailed investigation of clinical trials, we searched the literature (PubMed, Google Scholar and ScienceDriect) for preclinical data on changes in the expression of RAS components in ovarian cancer tissues, and the impact of these abnormalities on patient outcomes. We used the following search terms: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), ACEI, ACE-I, ARB, ovarian, ovary, cancer, carcinoma, malignancy, tissue, cells, AT1R, ACE, angiotensin receptor, expression. The reference lists of the publications found were also

reviewed. We included pre-clinical in vitro and in vivo studies employing ovarian cancer cell lines, ovarian cancer animal models and immunohistochemical studies with ovarian tissue samples. To obtain further information, we searched The Cancer Genome Atlas (TCGA) databases covering ovarian cancer patients in the cohort of TCGA, TARGET and The Genotype-Tissue Expression (GTEx) projects. We used an online exploration tool Xena Functional Genomics Explorer to check the expression of angiotensin-converting enzyme (ACE) gene in normal tissue, primary tumour cells and metastatic disease [22].

Then, to extend the scope of our research, we used a simple in silico, structure-activity relationship (SAR) method to predict the cytotoxicity of ACE-Is against ovarian cancer cell lines. For this purpose, we employed a CLC-Pred 2.0 (Cell-Line Cytotoxicity Predictor) web application, accessed at http://www.way2drug.com/clc-pred/. It employed training datasets from the Developmental Therapeutics Program (DTP) NCI60, as well as from ChEMBL and PubChem databases. It was able to predict cytotoxicity against NCI60 cell lines based on structure-activity analysis at three different thresholds of GI_{50}: 100, 10 and 1 nM. Here, GI_{50} is the concentration of a drug at which cell proliferation is reduced by 50%. We investigated six common ACE-Is: benazeprilat, captopril, enalaprilat, perindoprilat, ramiprilat and trandolaprilat. Their chemical structures in SMILES format (available at pubchem.ncbi.nlm.nih.gov) were used as input for the analysis. The output yielded P_a and P_i values for each cell line, which corresponded to “probability of being active” and “probability of being inactive”, respectively. If the inequality $P_a > P_i$ was fulfilled, the compound was considered more likely to belong to the subclass of active compounds than inactive ones, based on the similarity of chemical structure [23].

Finally, to find information on effects of ACE-Is on cancer incidence as well as on platinum-based chemotherapy or antiangiogenic treatment in malignancy we searched PubMed, Google Scholar and ScienceDriect from 2000 to 2023 with the restriction to publications written in English. The search terms were the following: angiotensin-converting enzyme inhibitor, ACEI, ACE-I, angiotensin receptor blocker, ARB, cancer, oncology, tumor; carcinoma, malignancy, anticancer, platinum, cisplatin, VEGF, chemotherapy, antiangiogenic, ovarian, gynaecologic, incidence, survival. Studies involving ACE-Is or ARB plus platinum-based chemotherapy or antiangiogenic therapy versus platinum-based chemotherapy or antiangiogenic therapy alone were taken into consideration. Cancer incidence and chemoprevention studies were also included, but only those not covered by our previous publications [20, 21, 24, 25]. Special focus was given to gynaecological cancers. In this section the following types of papers were excluded: reviews, case reports, pre-clinical

studies, editorials, letters without sufficient data, and non-peer reviewed sources (e.g., author replies, conference and abstracts).

Results

Five publications (n = 5) on RAS components expression (namely AT1R and ACE) in ovarian cancer cells were found and discussed. Furthermore, based on TCGA datasets, the expression of ACE gene was established in normal ovarian tissue, primary ovarian tumour and in metastatic disease. It was demonstrated in Figure 2.

The obtained SAR prediction of ACE-Is' cytotoxicity against various ovarian cancer cell lines was demonstrated in Table 1.

Table 1. CLC-Pred 2.0 prediction of ovarian cell-lines cytotoxicity for selected angiotensin-converting inhibitors (ACE-Is) at different GI_{50} threshold

ACE-I	**A2780cisR**	**SK-OV-3 GI_{50} 1 nM**	**OVCAR-5 GI_{50} 1 nM**	**OVCAR-3 GI_{50} 1 nM**	**OVCAR-3 GI_{50} 10 nM**	**SK-OV-3 GI_{50} 10 nM**	**OVCAR-5 GI_{50} 10 nM**
	$P_a > P_i$*						
Benazeprilat	0.494	0.180	–	–	0.339	–	–
Captopril	0.548	0.265	0.277	0.264	0.356	0.396	0.354
Enalaprilat	0.441	0.235	0.246	0.267	0.366	0.387	0.314
Perindoprilat	0.659	0.165	0.186	0.174	-	0.241	0.218
Ramiprilat	0.479	0.166	0.154	0.146	0.197	0.192	0.184
Trandolaprilat	0.479	0.166	0.154	0.146	0.197	0.192	0.184

* P_a — probability "to be active", P_i — probability "to be inactive"; for all the results presented $P_a > P_i$.

As for clinical data, after screening the titles and abstracts of the potentially relevant studies, thirty-two papers (n = 32) met our eligibility criteria. Eight of them (n = 8) covered the aspect of ACE-Is use as adjuvants to platinum-based treatment, with four observational studies dedicated to ovarian cancer. Eleven reports (n = 11) regarded combination therapy of ACE-Is and anti-angiogenic agents in patients with multiple cancers. Three papers (n = 3) discussed the chemopreventive aspects of ACE-Is in gynaecological malignancies. Finally, ten reports (n = 10) showed the potentially detrimental effect of ACE-Is on general cancer incidence.

Discussion

ACE-Is as candidates for repurposing to ovarian cancer

At present there are many ACE-Is available, including benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril and zofenopril. They have been in clinical use for more than three decades as first-choice options in cardiovascular and renal diseases. Their fundamental mechanism of action involves attenuation of the RAS by competitive inhibition of the angiotensin-converting enzyme (ACE) and downstream abolishment of angiotensin II (ANGII). Consequently, cardiovascular and renal normalization is achieved [24]. Besides maintaining homeostasis, RAS also regulates cellular functions, including proliferation, migration and angiogenesis. This sets the connection between RAS, ACE-Is and malignancy [20, 25]. Indeed, ACE-Is were previously shown to induce anti-proliferatory, anti-angiogenic, anti-inflammatory and pro-apoptotic cellular responses under a broad number of neoplastic conditions reviewed earlier [20, 21, 25]. These included: squamous cell carcinoma of skin, pancreatic cancer, hormone-refractory prostate cancer, myeloma, laryngeal, renal cell cancer, gastric, ovarian and cervical cancer [21, 25]. In addition, in many cancers the response to ACE-Is was correlated with AT1R overexpression, which in some cases corresponded with more aggressive tumour features and poor patient outcomes [20, 21, 25, 26]. Therefore, the repurposing of ACE-Is to oncology was deemed possible.

Our current literature screening for preclinical justification of ACE-Is use in ovarian neoplasms showed that in ovarian cancer a strikingly high frequency of AT1R expression occurs relative to normal tissue. In fact, the immunohistochemical staining of 99 ovarian tissue samples confirmed that AT1R was present in the majority of invasive ovarian carcinoma, while on surface epithelium of normal ovaries this receptor was actually absent [27]. Furthermore, the expression of AT1R dramatically increased with tumour progression from benign to malignant phenotypes, supporting a role of AT1R in ovarian cancer development [27, 28]. Besides, ACE turned out to be another component of abnormal ovarian RAS that was overexpressed by ovarian tumour stroma. Thus, it seems that ovarian cancer is capable of generating ANGII independently of the host system, providing a sufficient supply of effector molecules for stimulatory AT1R signalling. This assumption was confirmed in a study with 41 epithelial ovarian cancer patients [27, 29]. Consistently, also data available from the cohort of TCGA, TARGET and GTEx projects clearly indicated that the level of ACE gene expression in primary and recurrent ovarian tissues was significantly increased compared to normal ovarian tissue [22]. The above relationship was demonstrated in Figure 2. Furthermore, in the studies involving immunohistochemical staining of 166 ovarian tissue

samples and reverse transcription polymerase chain reaction (RT-PCR) analysis of ovarian SKOV-3 cells lines, aberrant RAS was shown to amplify local pro-inflammatory, pro-angiogenic and pro-migratory, but not pro-proliferatory cell responses [27, 28]. Thus, it can be concluded that RAS mediates rather indirect stimulation of ovarian cancer cells by promoting their migration and vascular growth during angiogenesis. Indeed, local overexpression of AT1R was positively correlated with VEGF and microvessel density. Of note, VEGF is a known signal cytokine driving ovarian cancer progression by neovascularization and ascites formation. Interestingly, the relationship between RAS and VEGF could contribute to the development of platinum resistance via the mechanism of abnormal vasculature formation and decreased cytotoxic drug penetration [27, 30]. Consistently with these observations, overexpression of RAS components, mainly AT1R, in ovarian tumours corresponded with worse patient prognosis (shorter PFS and OS, $p = 0.041$ and 0.017, respectively) and higher mortality rates compared to matched individuals manifesting negative AT1R status [30]. Therefore, there is a theoretical rationale behind targeting RAS in adjuvant ovarian cancer treatment. This idea was additionally supported by the fact that ARB, candesartan reversed the release of VEGF in ovarian cancer SKOV-3 cells. Of note, in this model, VEGF was initially stimulated by ANG II. In addition, candesartan suppressed tumour dissemination and neovascularization in a mouse model of peritoneal carcinoma *in vivo* [27]. Besides, another AT1R blocker, telmisartan, enhanced apoptosis of ovarian cancer cells by upregulating peroxisome proliferator-activated receptor (PPAR) and downregulating matrix metalloproteinases 9 (MMP-9). Typically, MMPs are required for ovarian cancer invasion, as they catalyse type IV collagen degradation in basement membrane and extracellular matrix [31]. The preclinical data on specific ACE-Is effect on ovarian cancer models were, however, unavailable. Also, studies showing no effect of ARBs were not published.

Therefore, we performed an in silico simulation using CLC-Pred 2.0 web application for predicting human cell line cytotoxicity based on structural features of compounds tested. We found that all ACE-Is could actually be active against the variety of ovarian cancer cells. The responsive models identified in our simulation included: A2780cisR (cisplatin-resistant ovarian carcinoma), A2780S (ovarian endometrioid adenocarcinoma), SK-OV3, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, IGROV1, NCI/ADR-RES and PA-1 at GI_{50} threshold of 1nM and 10 nM [23]. The compounds with the highest probability of being cytotoxic were demonstrated in Table 1. Notably, they were also likely to be active against platinum-resistant cells, which further supports our research hypothesis. To conclude, the available experimental

evidence consistently supports the idea of ACE-Is repurposing, yet the dedicated confirmatory studies are still needed.

The discussed preclinical data were with agreement with the reviewed clinical observations form studies specifically addressed to ovarian cancer, as well as from reports on overcoming platinum resistance in other malignancies. For example, an increased OS in patients treated with platinum-based chemotherapy plus ACE-Is versus chemotherapy alone was found in the following neoplasms: advanced non-small-cell lung cancer (OS improved by 3 months) [32, 33], advanced gastric cancer (OS improved by 5,7 months) [34] and metastatic colorectal cancer (OS improved by 11 months) [35]. Here, the platinum-sensitizing properties of ACE-Is probably resulted from the attenuation of VEGF [36]. Consistently, a meta-analysis of seven retrospective observational studies, in patients with non-small cell lung cancer, advanced pancreatic cancer, advanced gastric cancer, invasive primary breast cancer and metastatic renal cell carcinoma (n = 2,436), showed improved PFS and OS for the combination of standard chemotherapy and ACE-I or ARB compared to chemotherapy alone [OS: hazard ratio (HR) = 0.80; 95% confidence interval (CI): 0.69–0.92; PFS: HR = 0.79, 95% CI: 0.66–0.94]. The beneficial outcomes were the most pronounced in the subgroup treated with platinum compounds with anti-RAS adjuvant (HR = 0.56, 95% CI: 0.38–0.82) [37]. Therefore, it seems that ACE-Is in combination with platinum constitute the most promising chemotherapeutic protocol to be extrapolated to other vulnerable malignancies, such as ovarian cancer. Furthermore, ACE-Is co-administered with anti-VEGF agents, also improved survival in metastatic renal cell cancer [38–40], metastatic colorectal cancer [35, 41], glioblastoma [42], advanced hepatocellular carcinoma [35] and non-small cell lung cancer [43, 44] probably through their additive antiangiogenic activity. On the contrary, in a secondary pooled analysis of two phase III randomized controlled trials, RAS-modulating agents had no effect on survival of metastatic renal cell carcinoma patients treated with anti-VEGF agents [45]. Also, in a group of patients with different cancers (gastric, colorectal, lung and liver) the time-to-treatment failure was not superior when anti-RAS agents were added to anti-VEGF treatment [46]. These observations indicate that the synergistic antiangiogenic activity of ACE-I and targeted treatments is not universal across cancers and patient populations.

As for ovarian cancer specifically, only four observational studies performed in Asian, American and Finnish populations were found. Firstly, Min Ae Cho et al. reported increased survival in patients from South Korea treated with standard chemotherapy plus ARB (PFS 37.8 months) versus chemotherapy alone (PFS 33,6 months) (HR = 0.65, 95% CI: 0.42–0.99)

[47]. Similarly, two independent research groups from the United States, viz: Huang et al. and Harding et al., observed reduced mortality in ovarian cancer patients treated with ACE-Is plus chemotherapy versus chemotherapy alone in the post-diagnosis setting (HR = 0.53, 95% CI: 0.31, 0.91 and aHR = 0.76, 95% CI: 0.63–0.92) [48, 49]. Zhao et al., in turn, showed increased OS in patients using ACE-I/ARB combined with chemotherapy relative to those using other hypotensives plus chemotherapy (median 63 months vs 33 months; HR = 0.55, 95% CI: 0.36–0.94) [50]. Finally, in the Finnish population, a reduced, dose-dependent 10-year mortality (HR = 0.92, 95% CI: 0.87–0.98) was depicted in ovarian cancer patients undergoing chemotherapy together with ACE-Is. Notably, in this study, for the maximum ACE-I doses the mortality was the lowest (HR = 0.84, 95% CI: 0.77–0.92) [51]. These findings clearly set the rationale for a more comprehensive investigation in this area.

On the other hand, the reports on prophylactic application of ACE-Is in gynaecologic malignancies provided conflicting results. For instance, in a large population-based case-control study (n = 488,680) using Taiwan's Health and Welfare Data Science Centre database, the anti-RAS strategies were generally associated with a significantly decreased risks of female-specific cancers. In subgroup analysis, however, chemoprevention was evident for cervical (aOR = 0.79, 95% CI: 0.74–0.84) and ovarian cancer (aOR = 0.81, 95% CI: 0.79–0.84), but for endometrial cancer the risk was strikingly increased (aOR = 1.06, 95% CI: 1.01–1.11) [52]. On the contrary, two other research groups reported no correlation between pharmacological suppression of RAS and gynaecologic cancers incidence, including ovarian, uterine cancer [53, 54]. This discrepancy clearly emphasized a need for a greater scientific effort to define the role of ACE-Is in ovarian malignancy more precisely. Here, the report on increased endometrial cancer risk was particularly disturbing and it must be clarified as a priority. In fact, such an association could pose a significant barrier for further development perspectives of ACE-Is. Hence, the aspects of potential pro-carcinogenic toxicity of these drugs will be discussed in more detail in the following paragraph.

ACE-Is as potential cancer causative factor

Despite substantial data supporting the idea behind possible adjuvant application of ACE-Is in ovarian cancer, there are also accumulating reports which considerably complicate the understanding of these drugs in malignancy. In our research we, actually, found several studies which surprisingly suggested that chronic use of high doses of ACE-Is may translate into an increased cancer risk. For instance, a meta-analysis of 41 observational studies, showed that the activity of ACE-Is varies across tumour types. Here, an increased risk of

melanoma, kidney and female reproductive cancers was shown in ACE-I users, while in a subgroup of breast, lung, oesophagus, stomach, colon and rectal cancer, the incidence was decreased. Also, in all cancer group the overall risk was reduced [54]. Other research team, in turn, reported an increased risk of melanoma [relative risk (RR): 1.09, 95% CI: 1.00–1.19] and kidney cancer (RR: 1.50, 95% CI 1.01–2.23) in ACE-I-treated patients, but a decreased risk of oesophageal cancer (RR: 0.73, 95% CI: 0.57–0.94) [55]. Furthermore, a reduced survival from malignant diseases among hypertensive individuals emerged in two randomized controlled trials: with enalapril (OR = 1.59, 95% CI: 0.90–2.820) and benazepril (OR = 1.52, 95% CI: 0.45–5.42). Their meta-analysis, including 1,585 ACE-I users and 1,567 ACE-I non-users confirmed these observations with a pooled OR = 1.57 (95% CI 0.97-2.57) [56]. Similarly, in multiple myeloma, OS and PFS were worse in ACE-I treated hypertensive patients relative to non-ACE-I-treated group (OS: 38.7 vs. 73.3 months after diagnosis; p = 0.025; PFS 19.3 *vs.* 48.6 months; p = 0.041) [57]. In breast cancer, in turn, ACE-Is showed protective properties against primary disease [54]; however, they were associated with cancer recurrence. For example, in Washington State and Idaho population (US), a higher incidence of a second breast cancer was related to ACE-Is use, specifically in a post-diagnosis period (HR = 1.66, 95% CI: 1.06–2.58) [58]. Furthermore, in a nationwide prospective cohort of Danish breast cancer survivors, ACE-Is, mainly enalapril and ramipril, were associated with an increased rate of breast cancer relapse (HR = 1.2, 95% CI: 0.97–1.4) [59]. Finally, in The Life After Cancer Epidemiology Study cohort, a significantly increased hazard of breast cancer recurrence correlated with ACE-Is treatment within period of one year before and after diagnosis (n = 137, HR = 1.56, 95% CI: 1.02–2.39, p = 0.4). Here, statistical significance persisted even after adjusting for hypertension occurrence (HR = 1.77, 95% CI: 1.10–2.85, p = 0.02) [60]. In addition to this, lung cancer studies provided similar alarming results. Firstly, basing on four Danish health registries, Kristensen et al. established that the exposure to high cumulative ACE-I doses (above 3,650 defined daily doses) translated into 33% increased odds of lung tumour development (aOR: 1.33, 95% CI: 1.08–1.62). Simultaneously, the doses below this threshold showed neutral associations. The researchers concluded that, given high prevalence of ACE-Is' use, the observed modest increase in cancer hazard potentially translates into a significant absolute number of individuals at risk [61]. These results were confirmed by Hicks et al. who analysed data from UK Clinical Practice Research Datalink. Their results clearly demonstrated that the hazard of lung cancer was increased in ACE-Is users treated with ramipril, lisinopril and perindopril for more than 5 years (HR = 1.22, 95% CI: 1.06–1.40) [62]. Consistently, Asian patients treated with ACE-Is were found to have a

significantly higher risk of lung cancer for exposure duration exceeding 45 days per year (aHR = 1.87, 95% CI: 1.48–2.36) or 540 defined daily doses per year (aHR =1.80, 95% CI: 1.43–2.27) [63]. On the contrary, the most recent systematic review and meta-analysis by Bahaj et al. suggested that there was no significant link between ACE-Is and lung malignancy [64]. Therefore, the mechanisms by which ACE-Is could affect cancer initiation and progression remain obscure. However, they must not be ignored.

Root cause of concern

Consequently to the existing uncertainty on ACE-Is' safety, the anticipated repurposing of these drugs must be preceded by a dedicated risk/benefit analysis. With this respect, several interesting clues deserve scientific attention. Firstly, the putative cancer-inducing activity of ACE-Is is not organ-specific. As demonstrated above, it was actually moderate in potency and random across different cancers. Hence, their potential mechanism of carcinogenicity seems to be contextual. Moreover, these side effects manifested themselves only after long-term therapy with high doses. In short treatment, in turn, ACE-Is were relatively safe. Hence, the cumulative exposure to these drugs seems to be of importance, meaning that they can be genotoxic. In this context, a DNA-reactivity of ACE-Is' and their formulation components should be considered, with a special attention on potential genotoxic impurities. Our postulate is supported by a recent global crisis in pharmacy caused by genotoxic nitrosamine contaminants, which were initially discovered in ARB-containing products in 2018. This event initiated the ongoing global safety re-evaluation process, that to date has resulted in the recall of more than 1,800 affected batches of various pharmaceuticals. They included antidiabetics, antihistamines, antibiotics and, betablockers in the Unites States only [65]. Crucially, the mutagenic N-nitrosamine contamination was not recognised during legal drug assessment. Hence, it was revealed that the regulatory requirements for safety assurance of marketed medicines were insufficient. In the European Union, the deficiencies regarded ICH M7 (R1) safety guideline *Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*. Its primary problem was a limited scope of application, which mainly covered new drugs submitted after 2014. Thus, older pharmaceuticals, such as ACE-Is and ARBs, remained unverified in the safety aspect in question [66–69]. Interestingly, for the pharmacologically allied ARBs, the suggestions on their potential carcinogenicity were available even before the nitrosamine crisis. Then their contamination was confirmed, yet a causal link between nitrosamine impurities and cancer incidence among ARBs users could have not been established [70]. By close analogy, similar

concerns might apply to ACE-Is. Theoretically, the presence of nitroso-contamination in ACE-Is used in clinical trials could considerably affect patient outcomes and lead to positive associations with cancer incidence. Therefore, establishing whether mutagenic impurities physically reside in ACE-Is dosage forms could possibly clarify the role of these drugs in malignancy.

Here, it must be also noted that the sources of mutagenic drug impurities are multiple. Technologically, they can be residue from the synthesis and formulation process or appear secondary to drug degradation [71–73]. This type of impurity is less problematic because, once qualified and quantified, it can be effectively controlled [71]. Of more concern are mutagenic N-nitroso derivatives formed *in vivo* from nitrosatable drug precursors and nitrite in the acidic solution of gastric juice. The resulting drug-nitrite interaction products can be enzymatically converted to reactive species and then participate in electrophilic chemical reactions with DNA in all host tissues, initiating carcinogenesis (Fig. 3). In this context, N-nitroso metabolites may originate from molecules containing amine, amide, cyanamide, guanidine, hydroxylamine, amidine, hydrazine, hydrazide, piperazine and diketopiperazine structural alerts. Such compounds constitute a significant proportion of the existing drugs, confirming prevalence of the problem [64, 71]. With this respect, the identification of N-nitrosation potential for drugs with structural alerts should be performed by appropriate *in vitro* and *in vivo* assays.

Conclusion

Taking all the above into consideration, there is a real problem with ovarian cancer management due to sustained insufficiency of pharmacotherapy and inadequate level of innovation, translating into poor survival statistics. Hence, screening for platinum-sensitizers among existing pharmaceuticals seems to be an attractive strategy of providing more efficient therapeutic options. ACE-Is could offer a wide range of advantages in this field, given their pleiotropic anticancer and adjuvant activity. Numerous preclinical and clinical studies supported the concept of their repurposing. However, their beneficial effects are countered by their putative pro-carcinogenic potential, which sets the barrier for further development and requires immediate scientific response. Therefore, the verification of the existing alarming observations by appropriate *in vitro* and *in vivo* assays has emerged as a high-priority intervention to ensure overall patient safety. In this context, the genotoxic impurity profiling is a direction that could offer a conclusive proof of their real role in malignancy. For this reason,

we propose that dedicated mutagenicity, genotoxicity and vulnerability to nitrosation assays should be performed urgently.

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Authors' contributions

Conceptualization: K.R.; methodology: K.R.; investigation: K.R.; writing — original draft preparation: K.R.; writing — review and editing: K.R., M.M., T.K., J.K.M., KG; visualisation: T.K., K.R.; supervision: B.S.; funding acquisition: K.R. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Availability of data and materials

The datasets used during the current study are available online or from the corresponding author on reasonable request.

Ethics approval

All data is available online, access is unrestricted and does not require other permissions. The use of the data does not violate the rights of any person or any institution.

Consent for publication

All authors read and approved the final manuscript.

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Figure 1. The mechanisms of platinum resistance in ovarian cancer: **A.** Dysregulation of drug cellular transporters that cause reduced influx and increased efflux of platinum compounds; **B.** inactivation of platinum via endogenous formation of conjugates with glutathione and metallothionein; **C.** repair of the platinum-induced DNA damage by nucleotide excision repair, homologous recombination or non-homologous end-joining pathways, d) alternation of tumour microenvironment by excessive release of vascular endothelial growth factor (VEGF) and formation of abnormal blood vessels that reduce cytotoxic drug distribution, e) excessive infiltration of tumour-associated macrophages which promote survival, invasion and chemoresistance in a positive feedback loop

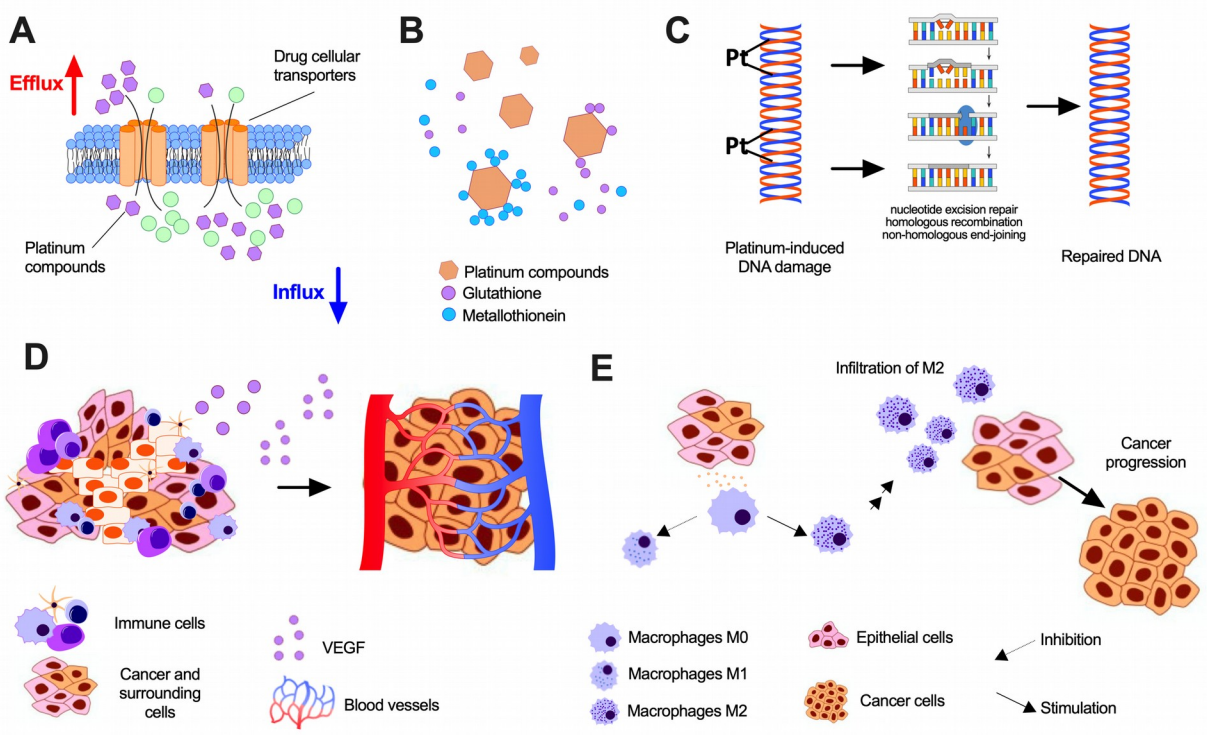


Figure 2. Increased expression of angiotensin-converting enzyme (ACE) gene in primary and recurrent ovarian cancer versus normal ovarian tissue

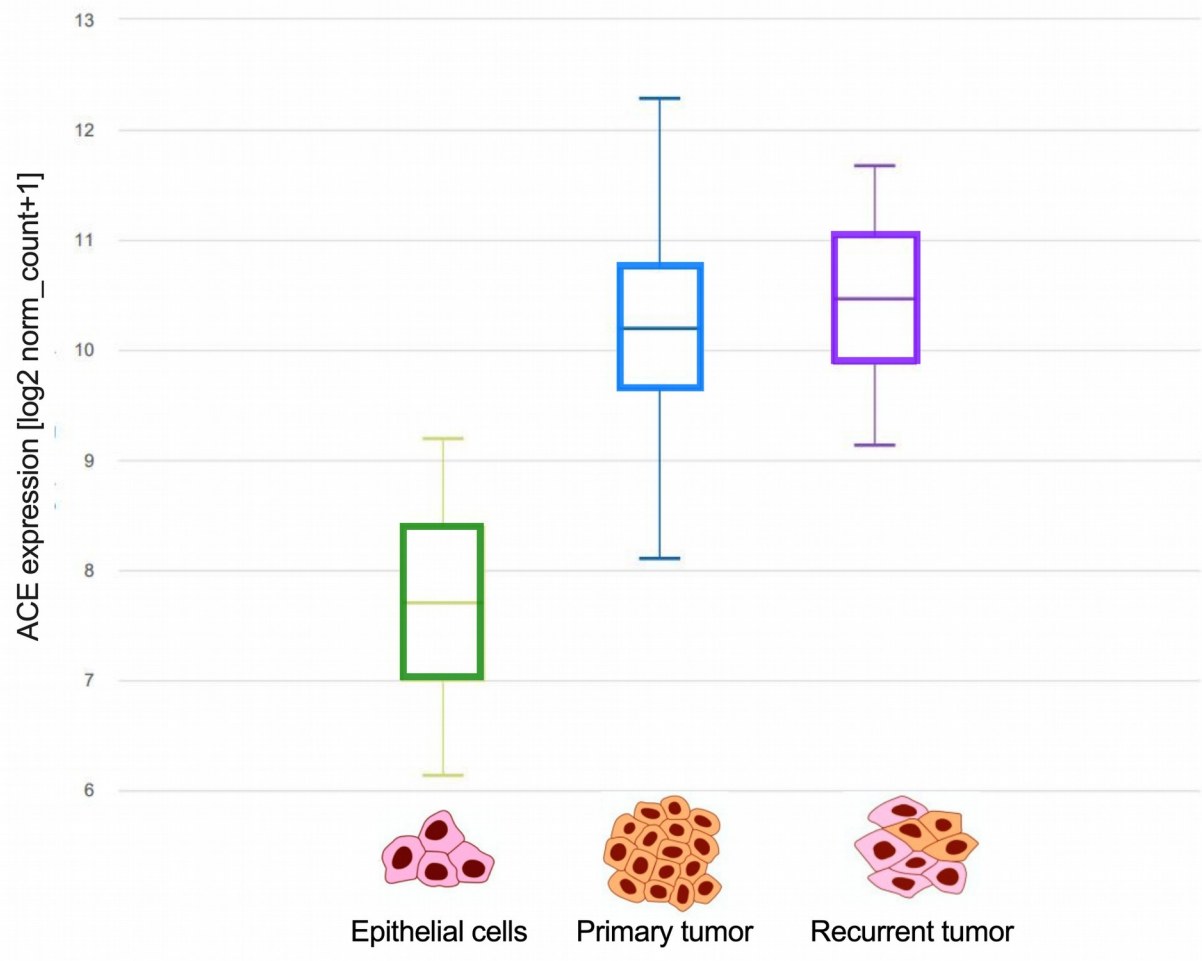
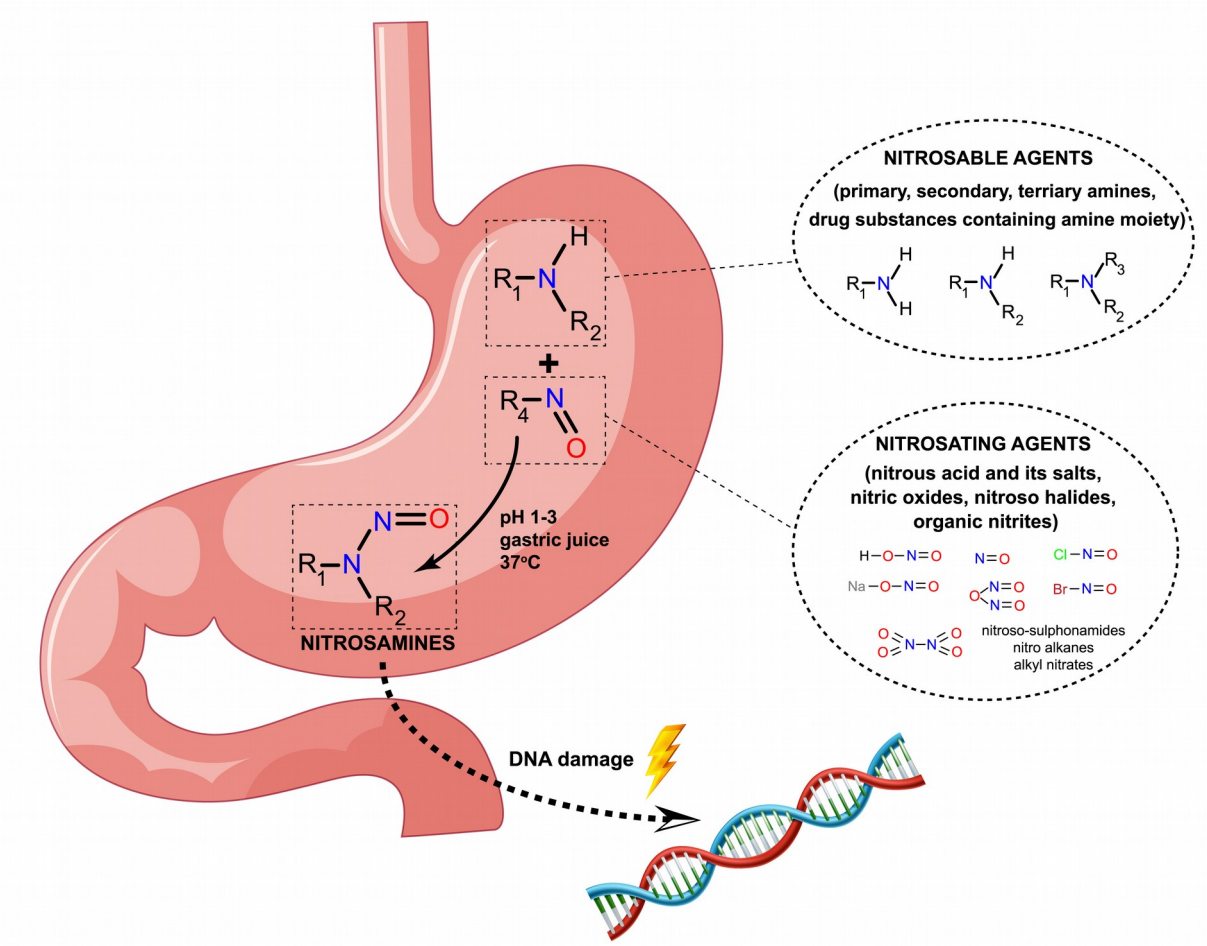


Figure 3. The mechanism of an endogenous drug nitrosation


NITROSABLE AGENTS
(primary, secondary, terriary amines,
drug substances containing amine moiety)
NITROSATING AGENTS
(nitrous acid and its salts,
nitric oxides, nitroso halides,
organic nitrites)
nitroso-sulphonamides
nitro alkanes
alkyl nitrates
pH 1-3
gastric juice
37°C
NITROSAMINES
DNA damage