Drug-related cancers: Analyses of head and neck cases reported in the literature

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Abstract

Background. Recent advances have attributed carcinogenic potential to pharmacotherapy. Cancers of the head and neck region are no exception.

Objectives. This descriptive investigation aimed to identify studies reporting on drugs that have contributed to cancer development in the head and neck region.

Material and methods. Online databases were searched for relevant articles and their data were summarized, including age, gender, main drug classification and name, additional drugs, primary disorders, drug-related cancers, and the site of each drug-related cancer.

Results. The mean age of the patients included in this analysis was 52.9 years. However, drug-related head and neck cancers (DR HNCs) were most prevalent in persons over 60 years of age. Overall, these cancers were more prevalent in females than in males (1.33/1). The HNC-related drugs could mainly be categorized into 3 groups, namely, immunomodulatory/immunosuppressive, chemotherapeutic and chemoprotective drugs, while the most frequently used additional drugs across the studies were corticosteroids. The 5 most prevalent primary conditions for which the patients had received pharmacotherapy were organ transplantations, lymphoproliferative disorders (LPD), rheumatoid arthritis (RA), Epstein–Barr virus (EBV) infection, and bone sarcoma. The most prevalent HNCs were squamous cell carcinoma (SCCs), thyroid cancers (including papillary and follicular thyroid carcinomas), LPD, and mucoepidermoid/acinic cell carcinomas, which occurred mostly in the oral cavity, neck, salivary glands, pharynx/larynx, and head/face.

Conclusions. This study was the first of its kind to analyze and discuss the aforementioned findings regarding the head and neck region in depth. Clinicians should familiarize themselves with DR HNC cases to effectively screen suspected patients.

Keywords: drugs, malignancy, pharmacotherapy, carcinogenesis, head and neck cancer

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Introduction

Carcinogenesis is defined as the transformation of normal cells into cancer cells, and can be attributed to a number of factors, including pharmacotherapy.[1–3] The therapeutic use of drugs may cause long-term toxicities[4] or immunosuppression,[5,6] which can facilitate cancer development. The subsequent malignancies may present as ulceration,[7,8] hyperplasia[9,10] or lymphoproliferative disorders.[5,11] Although drugs are tested in various ways to ensure their safety, they may not be safe for human use if carcinogenesis is taken into account.[12] This is because of the relatively non-specific nature of the tests which are used for determining drug toxicity.[13,14] Head and neck cancers (HNC) are no exception to drug-related (DR) cancers of the human body.[2,15]

Head and neck cancers are defined as cancers occurring within the mouth, pharynx, larynx, nose, paranasal sinuses, thyroid, parathyroid, salivary glands, and cervical esophagus; malignancies related to the skin in this region are also counted as HNCs.[16] Head and neck cancers are the 9th most prevalent malignancies, with over 650,000 cases worldwide each year.[17] Although risk factors for HNC, such as smoking,[18,19] alcohol consumption,[18,19] and human papillomavirus (HPV)[18,19] and Epstein–Barr virus (EBV)[19] infection have been recognized, the incidence of HNC has not decreased significantly in the USA,[20] Asia,[21,22] Europe,[23] or Australia[24] in recent years. Also, various kinds of treatment for these cancers are yet to be considered effective at eradicating the malignancies in case of late diagnosis.[25,26] Regarding the incidence and mortality rate, the importance of prompt diagnosis cannot be overemphasized; still, a timely diagnosis of HNCs with the use of the current measures is yet to be achieved.[27] Therefore, attention should be given to developing more efficient screening techniques and to their evaluation by the clinicians treating diseases of the head and neck region.[28] However, the lack of a holistic account of DR HNCs precludes success in this matter.

Objectives

The recognition of the drugs which have been reported to cause HNCs and their documented presentations may help clinicians identify patients at risk so that the subsequent screening procedures and management of these patients may be accomplished without troublesome complications. We considered an analysis of publications about drugs that can potentially induce HNCs helpful; thus, the current descriptive study was undertaken to answer the following question: "Which drugs have been reported to induce cancers in the head and neck region or increase their risk?" by analyzing publications about DR HNCs.

Material and methods

Online databases, namely, PubMed, Embase, Cochrane Library, and Web of Science, were searched for relevant articles without any past date restrictions published until March 2020. The following keywords were used in the search queries: "head", "neck", "cancer", "malignancy", "drug", "medication", "medicine", and "medicament". Thesaurus terms, such as "therapy-related cancer", "cancer of head and neck" and "head and neck neoplasms", were also used, according to the requirements of each database. In addition, journals with scope encompassing head and neck or oral oncology as well as the reference lists of relevant articles were also manually searched. Finally, complementary exploration was conducted in Google Scholar for articles related to the topic and those which cited studies relevant to drug-induced cancers. The obtained papers were screened by their titles and abstracts as well as by full texts in a stepwise manner. Eligible studies were determined as English-language case reports, case series, case–control studies, cohorts, randomized or non-randomized controlled studies, and longitudinal studies describing at least 1 drug which had resulted in HNC or had increased the risk of its development. Any studies with incomplete information, i.e., not mentioning the site of the newly developed cancer, the drug name or the type of cancer, were excluded. To exclude the outdated pharmacotherapeutic treatment protocols, we did not take into account studies published before January 2000. Finally, after a thorough search and screening process, 35 articles were included in this study. They comprised 30 case reports and case series, 3 longitudinal studies, 1 case–control study, and 1 cohort study. Table 1 presents a summary of the included studies sorted by the year of publication. Additionally, Fig. 1 depicts the flowchart of study selection and screening in detail.

The following data were extracted from the studies, where possible: author(s), year of publication, patients' age and gender, drug name and dosage, the primary disease for which the drug(s) were prescribed, type of cancer, cancer site, description of cases and control groups, odds ratios (*OR*s), and the significance of findings. To provide a better insight into the clinical characteristics of DR HNCs, we combined the data from all the included studies and analyzed them according to the assessed outcome, whenever possible. The assessed outcomes were age, gender, drug classification, drug name(s), additional drug(s), primary disorder(s), DR cancer, and its site. In case of absence of data in any of the studies regarding these outcomes, such study was excluded from the analysis. Table 2 presents the results of the combination of the data from all studies according to the aforementioned outcomes.

Table 1. Reported cases of drug-related head and neck cancers (DR HNCs) in the literature from January 2000 onward

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Sandoval and Jayabose[29]	2001	3	male	chemotherapeutic drug	cyclophosphamide	1,200 mg/m^2, 1 dose	daunomycin, vincristine, asparaginase, prednisone, cytarabine, MTX	ALL	MEC	parotid gland
Preciado, et al.[35]	2002	mean age: 53	–	immunosuppressant	prednisone (n = 23) and azathioprine (n = 22)	prednisone (7.22 mg/day) azathioprine (66.67 mg/day) (for those who survived >2 years)	–	solid organ transplantation	SCC (n = 23)	parotid gland (n = 8), oral cavity (n = 7), hypopharynx (n = 2), larynx (n = 2), neck (n = 2), lip (n = 1), nasal cavity (n = 1)
Kalantzis, et al.[77]	2005	72	female	immunosuppressant	MTX	–	–	RA, EBV+	polyclonal B cell lesion	upper jaw gingiva
Savelli, et al.[66]	2005	14	female	chemotherapeutic drug	cyclophosphamide	–	vincristine, daunomycin, prednisone, MTX, cytarabine	lymphoma of scalp	MEC	parotid gland
Savelli, et al.[66]	2005	14	female	chemotherapeutic drug	vincristine, prednisone, L-asparaginase, daunomycin, MTX	6 cycles as maintenance therapy	–	ALL	MEC	parotid gland
Acero, et al.[78]	2006	79	female	immunosuppressant	MTX	7.5 mg/week for 15 years	sulfasalazine	RA, EBV+	DLBCL	upper jaw gingiva
Becker, et al.[9]	2006	56	female	immunosuppressant	tacrolimus	0.1% ointment	–	lichen planus	SCC	tongue
Kojima, et al.[79]	2006	73	female	immunosuppressant	MTX	for several years	steroid therapy	RA, EBV+	PSLLPI	oral cavity
Muirhead and Ritchie[80]	2007	63	male	immunosuppressant	azathioprine	–	cyclosporine	liver transplantation	Merkel cell carcinoma	neck
Tebbi, et al.[4]	2007	–	–	chemoprotective drug (topoisomerase II inhibitor)	dexrazoxane	300 mg/m^2 intravenously	ABVE (doxorubicin, bleomycin, vincristine, and etoposide)	Hodgkin's disease	PTC	thyroid gland
Tanaka, et al.[81]	2008	44	male	immunosuppressant	MTX	10 mg/week	betamethasone	RA, EBV+	DLBCL	upper jaw gingiva
Uneda, et al.[82]	2008	70	male	immunosuppressant	MTX	2 mg/week for 6 years	prednisolone	RA, EBV+	DLBCL	upper jaw gingiva

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Hasserjian, et al.[83]	2009	72	female	immunosuppressant	adalimumab	for 7 years	MTX	RA	extranodal B cell lymphoma	right inferior orbital rim
Hasserjian, et al.[83]	2009	63	female	immunosuppressant	infliximab	for 5 months	MTX	Crohn's disease, arthritis	Hodgkin lymphoma	neck
Dojcinov, et al.[84]	2010	80	male	immunosuppressant	MTX	–	–	RA, EBV+	LPD	tongue
Dojcinov, et al.[84]	2010	60	female	immunosuppressant	MTX	–	–	RA, EBV+	LPD	lip
Kikuchi, et al.[85]	2010	69	female	immunosuppressant	MTX	6 mg/week for several years	–	RA, EBV+	LPD	upper jaw gingiva
Mattsson, et al.[86]	2010	46	male	immunosuppressant	tacrolimus (topical)	total 3 tubes of 30 mg each	acetonide triamcinolone	lichen planus	SCC	buccal mucosa
Cannon, et al.[69]	2011	76 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	SCC	tongue
Cannon, et al.[69]	2011	67 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	high-grade squamous dysplasia	sublingual
Cannon, et al.[69]	2011	71 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	SCC	tongue
Cannon, et al.[69]	2011	52 (at oral cancer diagnosis)	female	chemotherapeutic drug	pegylated liposomal doxorubicin	for at least 3 years	–	ovarian cancer	multifocal SCC	left retromolar trigone, hard palate, right buccal mucosa
Ben-David, et al.[68]	2013	59	female	chemotherapeutic drug	doxorubicin	total dose: 60 mg every 6–8 weeks	–	ovarian cancer	SCC	maxilla
Ben-David, et al.[68]	2013	59	female	chemotherapeutic drug	doxorubicin	standard ovarian cancer treatment protocol	–	Kaposi's sarcoma	SCC	maxilla
Güngör, et al.[87]	2013	50	male	immunosuppressant	pimecrolimus	cream	topical steroid	lichen planus	SCC	lip
Hanakawa, et al.[7]	2013	67	male	immunosuppressant	MTX	6 mg/week for 20 years	prednisolone – sodium aurothiomalate – diclofenac sodium	RA	LPD	oropharynx

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Ishida, et al.[88]	2013	76	female	immunosuppressant	MTX	for 10 years	infliximab, prednisolone	RA, EBV+	LPD	gingiva
Wimmer, et al.[36]	2013	–	–	immunosuppressant	cyclosporine ($n = 3$) and tacrolimus ($n = 3$)	cyclosporine (100–150 ng/mL) for 11 years tacrolimus (8–10 ng/mL) for 11 years	–	liver transplantation	oropharyngeal cancer ($n = 6$)	oropharynx ($n = 6$)
Orouji, et al.[30]	2014	84	female	chemotherapeutic drug	vismodegib	150 mg/day for 16 weeks	–	BCC, actinic keratosis	SCC	lower lip
Tokuyama, et al.[90]	2014	67	female	immunosuppressant	MTX	5–12.5 mg/week for 9 years	prednisolone, alendronate sodium hydrate	RA, EBV+	DLBCL	hard palate
Fabiano, et al.[10]	2015	74	female	kinase inhibitor	ruxolitinib	–	–	myelofibrosis	SCC	forehead, mandible
Hashimoto, et al.[91]	2015	74	female	immunosuppressant	MTX	total dose: 260 mg for 40 weeks	prednisolone	RA, EBV+	LPD	tongue
Hashimoto, et al.[91]	2015	74	female	immunosuppressant	MTX	total dose: 1,936 mg for 248 weeks	prednisolone, tacrolimus	RA, EBV+	LPD	tongue
Horie, et al.[89]	2015	60	male	immunosuppressant	MTX	8 mg/week for 12 years	prednisolone, folic acid, bucillamine	RA, EBV+	DLBCL	upper jaw gingiva
Longhi, et al.[70]	2015	13	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	13	male	chemotherapeutic drug	vincristine, doxorubicin, ifosfamide, cyclophosphamide, etoposide, dactinomycin	–	–	Ewing's sarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	10	female	chemotherapeutic drug	vincristine, doxorubicin, ifosfamide, cyclophosphamide, etoposide, actinomycin-D	–	–	Ewing's sarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	27	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	17	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	acinic cell carcinoma	submandibular gland

Author(s)	Year of publication	Age [years]	Gender	Main drug classification	Main drug name(s)	Dosage	Additional drug(s)	Primary disorder(s)	DR cancer(s)	Site(s) of DR cancer(s)
Longhi, et al.[70]	2015	11	female	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	parotid gland
Longhi, et al.[70]	2015	9	male	chemotherapeutic drug	MTX, cisplatin, doxorubicin, ifosfamide	–	–	osteosarcoma	MEC	submandibular gland
Miyashita, et al.[92]	2015	82	male	immunosuppressant	MTX	5 mg/week for 8 years	–	RA, EBV+	LPD	tongue
Saintes, et al.[67]	2015	76	male	chemotherapeutic drug	vismodegib	150 mg/day	–	BCC	SCC	left frontal
Saintes, et al.[67]	2015	82	female	chemotherapeutic drug	vismodegib	150 mg/day	–	BCC	SCC	left frontal
Saintes, et al.[67]	2015	49	female	chemotherapeutic drug	vismodegib	150 mg/day	cetuximab	sclerodermiform BCC	SCC	nasal pyramid
Xu, et al.[93]	2015	59	male	chemotherapeutic drug	lenalidomide	25 mg orally q.d. d1–21	bortezomib, doxorubicin, dexamethasone	multiple myeloma	NPC	nasopharynx
Spiliopoulou, et al.[71]	2016	42	male	chemotherapeutic drug	bleomycin, cisplatin	3 cycles	etoposide	malignant undifferentiated teratoma	papillary carcinoma	thyroid gland
Spiliopoulou, et al.[71]	2016	27	male	chemotherapeutic drug	bleomycin, cisplatin	2 cycles	etoposide	malignant undifferentiated teratoma	papillary carcinoma	thyroid gland
Spiliopoulou, et al.[71]	2016	36	male	chemotherapeutic drug	bleomycin, cisplatin	2 cycles	etoposide	mixed germ cell tumor	papillary carcinoma	thyroid gland
Tao, et al.[6]	2017	–	–	immunosuppressant	rituximab	–	chemo- and radiation therapy	DLBCL	thyroid cancer ($n = 23$)	thyroid gland ($n = 23$)
Chambon, et al.[94]	2018	6	female	immunosuppressant	nivolumab	3 mg/kg injection every 2 weeks	2 courses of chemotherapy (5-fluorouracile 100 g/m^2 per day for 5 days and cisplatin 100 mg/m^2 per day for 1 day)	xeroderma pigmentosum	sarcomatoid carcinoma (SCC)	scalp
Lavacchi, et al.[95]	2018	82	male	immunosuppressant	nivolumab	3 mg/kg as 2nd line treatment for 7 cycles	vinorelbine	lung adenocarcinoma	Merkel cell carcinoma	upper eyelid
Niimi, et al.[5]	2019	63	female	immunosuppressant	MTX	8 mg/week	–	RA	LPD	palate

MTX – methotrexate; q.d. – quaque die (every day); ALL – acute lymphoblastic leukemia; RA – rheumatoid arthritis; EBV+ – Epstein–Barr virus-positive; BCC – basal cell carcinoma; DLBCL – diffuse large B cell lymphoma; MEC – mucoepidermoid carcinoma; SCC – squamous cell carcinoma; PSLLPI – polymorphous small lymphocytic lymphoplasmacytic infiltrate; PTC – papillary thyroid carcinoma; LPD – lymphoproliferative disorders; NPC – nasopharyngeal carcinoma.

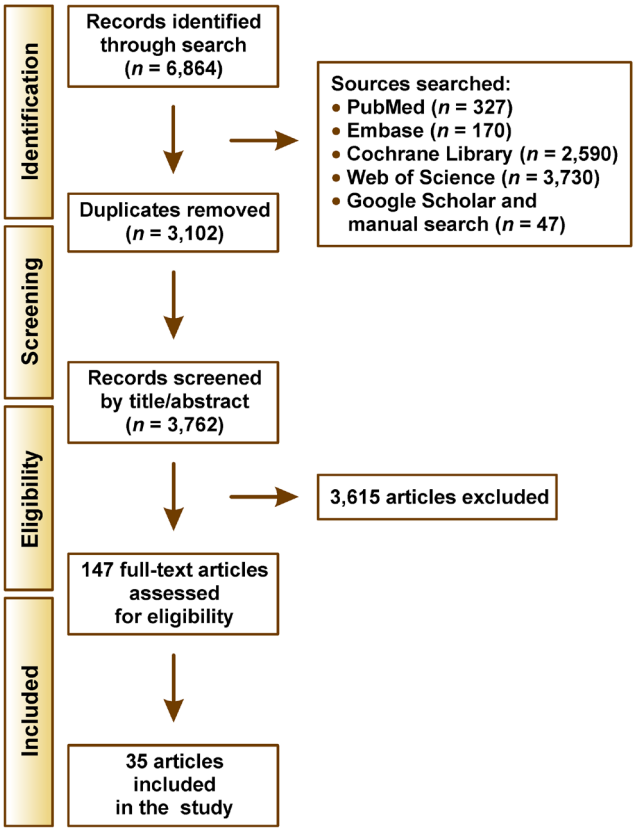

Fig. 1. Search flowchart

Results and discussion

We hereby discuss the most significant findings with regard to each outcome presented in Table 2.

Age

The lowest reported age for DR HNCs was 3 years,[29] while the highest reported age was 84 years.[30] Similar cancer incidences were found in the 1st (<40 years) and 2nd (40–60 years) age groups. However, the relative frequency of cancer incidence in the 3rd group (>60 years) was nearly twice as high as in other groups. This finding is in agreement with the latest statistics of the Surveillance, Epidemiology, and End Results (SEER) program, which also reports higher cancer rates in the older population.[31] However, the relative frequencies of HNCs in the first 2 age groups in this program were much higher than those reported in the present survey. This possibly reflects the nature of DR cancers; drugs damage the genes related to the cancer-associated pathways, as opposed to the chronic accumulation of aberrant genetic and epigenetic changes, which are related to the pathogenesis of ordinary cancers.[32,33] A potential implication of this finding, despite the limitations imposed by the type and number of studies, is that screening for DR HNCs should be implemented in a variety of age groups, conversely to the conventional screening procedures, which mainly screen the older-adult population.[34] The mean age of patients at the time of diagnosis of DR HNCs was 46 years for males and 58 years for females. However, the mean age for the total number of cases of DR HNCs was 52.9 years. The difference between the mean age values for males, females and all cases in total could be explained by different total numbers of cases in each of these groups (21, 28 and 72, respectively). This difference between the numbers of the reported cases arose from the data inadequacy of some studies regarding the gender specifications of the HNC patients.[4,6,35–37] The values of the reported mean age are lower than those reported for ordinary HNCs,[38] which might hint at the role of drugs in inducing HNCs.

Gender

Although we attempted to classify the reported outcomes by gender specifications, we could not achieve this, as most of the data regarding gender were incomplete or ambiguous. Thus, the only outcome which could be classified by gender was the patients' age.

Regarding the total relative frequencies, the female/male ratio of the diagnosed DR HNCs was 1.33/1, which is contrary to the ratios reported for ordinary cancers, which occur more frequently in males than in females.[38]

Table 2. Summary of the data combined from the included studies regarding specific outcomes

Specific outcome			Frequency (*n*)	Relative frequency* [%]
Age [years]	<40	male [29,70,71]	8	16.3
		female [66,70,94]	5	10.2
	40–60	male [71,81,86,87,89,93]	6	12.2
		female [9,67–69,84]	6	12.2
	>60	male [7,67,80,82,84,92,95]	7	14.3
		female [5,10,30,67,69,77–79,83,85,88,90,91]	17	34.7
	total		**49**	**100.0**
Gender	male		21	42.9
	female		28	57.1
	total		**49**	**100.0**

A closer look at the data reveals that DR HNCs occurred in females slightly more often in the 2nd than in the 1st age group, as can be expected by taking account of the statistics of human papillomavirus (HPV)-negative HNCs.[39] However, an interesting finding was that DR HNCs occurred approx. twice as often in females than males in the 3rd age group. This finding may partly be explained by the shorter life expectancy of males in comparison with females, which results in a higher number of surviving senile females.[40] Additionally, the most frequently used drug in this age group was methotrexate (MTX), which has been shown to incur higher acute toxicities in women than men,[41] suggesting that sex-specific differences can also be a factor in determining adverse outcomes. Moreover, higher clearance rates of drugs such as ruxolitinib,[42] doxorubicin[43] and adalimumab[44] have been reported in males than females, which may contribute to increased morbidity in females. These findings could indicate that females may have a higher propensity for developing DR HNCs in older age, yet data on this matter remains limited.

Main drugs (classification and names)

Cancer-related drugs in the included studies could mainly be classified into 3 groups, namely, immunomodulators/immunosuppressants, and chemotherapeutic and chemoprotective drugs. The 5 most prevalent drugs in the immunomodulator/immunosuppressant group were corticosteroids, azathioprine, rituximab, MTX, and tacrolimus. The 5 most prevalent cancer-related drug prescriptions in the chemotherapeutic group were doxorubicin, cisplatin, ifosfamide, MTX, and cyclophosphamide. Only 1 study, in which dexrazoxane was used, evaluated the effects of chemoprotective drugs on cancer development.[4]

Predictably, carcinogenic potential has been shown for most of the aforementioned drugs, namely, azathioprine,[45] cyclosporine,[46] doxorubicin,[47,48] cyclophosphamide,[49] cisplatin,[50] ifosfamide,[51] and dexrazoxane.[52] However, carcinogenicity was not the only modality by which these drugs could have contributed to the development of secondary cancers. It has been shown that

Specific outcome			Frequency (*n*)	Relative frequency* [%]
Main drug classification and names	immunosuppressant	corticosteroid [35,66]	24	15.4
		azathioprine [35,80]	23	14.7
		rituximab [6]	23	14.7
		methotrexate [5,7,77–79,81,82,84,85,88–92]	16	10.3
		tacrolimus [9,36,86]	5	3.2
		cyclosporine [36]	3	1.9
		nivolumab [94,95]	2	1.3
		pimecrolimus [87]	1	0.6
		total	**97**	**62.2**
	chemotherapeutic drug	doxorubicin [68–70]	13	8.3
		cisplatin [70,71]	8	5.1
		ifosfamide [70]	7	4.5
		methotrexate [66,70]	6	3.8
		cyclophosphamide [29,66,70]	4	2.6
		vismodegib [30,67]	4	2.6
		bleomycin [71]	3	1.9
		vincristine [66,70]	3	1.9
		etoposide [70]	2	1.3
		actinomycin-D [70]	1	0.6
		adalimumab [83]	1	0.6
		dactinomycin [70]	1	0.6
		daunomycin [66]	1	0.6
		infliximab [83]	1	0.6
		L-asparaginase [66]	1	0.6
		lenalidomide [93]	1	0.6
		ruxolitinib [10]	1	0.6
		total	**58**	**37.1**
	chemoprotective drug	dexrazoxane [4]	1	0.6
	total		**156**	**99.9**

corticosteroids[53] and rituximab[54,55] can inhibit the immune function, thus disrupting the normal immune system surveillance. Furthermore, it has been demonstrated that MTX, despite its immunosuppressive properties, is not associated with an increased cancer risk.[56,57] However, it was the 4th most frequently used drug in the immunodulator/immunosuppressant group. Furthermore, we found an additional controversy regarding the use of oral contraceptives. Although in a study by Grevers et al. the relationship between an increased thyroid cancer risk and the use of oral contraceptives was shown in the primary analysis, additional analyses proved that after adjusting for various other factors, their use was not associated with an increased thyroid cancer risk.[58] Additionally, studies have shown that while the use of oral contraceptives can increase the risk of various cancers,[59] their effects on thyroid cancer development are disputable.[60–62] Due to inconsistent results regarding the use of oral contraceptives, we chose to exclude this type of drugs from our study. Such controversial findings warrant further research, yet it may be hypothesized that the many confounding variables which were present across the studies, e.g., age, predisposing conditions and co-carcinogens, might have contributed to DR HNCs development. Future research should describe the pathways by which these drugs may cause cancers, especially HNCs.

Additional drugs

As could be expected, additional drugs were similar to the main drugs analyzed in the included studies. The most prevalent additional drugs used in the studies were corticosteroids. The role of additional drugs in cancer development may be described as either facilitating cancer growth, as can be seen with the use of corticosteroids, or exacerbating cancer development, as can be observed with the use of cytotoxic drugs. Additionally, drug interactions might have also occurred in these studies, which could further contribute to the problem.

Primary disorders

From a clinical perspective, recognizing the conditions which may predispose a patient to secondary cancers, either due to their inherent characteristics

	Specific outcome	Frequency (*n*)	Relative frequency* [%]
Additional drugs	corticosteroid [7,29,66,81,82,86–91,93]	14	28.6
	methotrexate [29,66,83]	4	8.2
	etoposide [4,71]	4	8.2
	vincristine [4,29,66]	3	6.1
	cytarabine [29,66]	2	4.1
	daunomycin [29,66]	2	4.1
	doxorubicin [4,93]	2	4.1
	acetonide [86]	1	2.0
	alendronate sodium [90]	1	2.0
	asparaginase [29]	1	2.0
	bleomycin [4]	1	2.0
	bortezomib [93]	1	2.0
	bucillamine [89]	1	2.0
	cetuximab [67]	1	2.0
	cisplatin [94]	1	2.0
	cyclosporine [80]	1	2.0
	diclofenac sodium [7]	1	2.0
	folic acid [89]	1	2.0
	5-fluorouracil [94]	1	2.0
	hydrate [90]	1	2.0
	infliximab [88]	1	2.0
	sodium aurothiomalate [7]	1	2.0
	sulfasalazine [78]	1	2.0
	tacrolimus [91]	1	2.0
	vinorelbine [95]	1	2.0
	total	**49**	**99.4**

	Specific outcome	Frequency (*n*)	Relative frequency* [%]
Primary disorders	organ transplantation [35,36,80]	30	25.4
	LPD** [4,6,66,93]	26	22.0
	rheumatoid arthritis [5,7,77–79,81–85,88,89,91,92]	17	14.4
	EBV+ [77–79,81,82,84,85,88–92]	14	11.9
	bone sarcoma [70]	7	5.9
	ovarian cancer [68,69]	5	4.2
	basal cell carcinoma [30,67]	4	3.4
	lichen planus [9,86,87]	3	2.5
	testicular cancer [71]	3	2.5
	leukemia [29,66]	2	1.7
	actinic keratosis [30]	1	0.8
	arthritis [83]	1	0.8
	Crohn's disease [83]	1	0.8
	lung adenocarcinoma [95]	1	0.8
	myelofibrosis [10]	1	0.8
	soft tissue sarcoma [68]	1	0.8
	xeroderma pigmentosum [94]	1	0.8
	total	**118**	**99.5**

or their pecific treatment, may be helpful when screening patients for DR HNCs. The 5 most prevalent conditions were organ transplantations, lymphoproliferative disorders (LPD), rheumatoid arthritis (RA), EBV infection, and bone sarcoma. As could be expected, these disorders were the predictors of the drug choices discussed in the previous sections. However, as the literature on DR HNCs is limited, clinicians should be aware of similar disorders when evaluating a patient. Additionally, screening by primary disorders may help with the diagnosis of more cases of HNC, as different therapeutic regimens may not include the drugs which are listed in this study as cancer inducers.

Drug-related cancers

Although previous studies have omitted thyroid cancers and LPD from their HNC categories,[63,64] we used the HNC definition provided by Holland et al.[16] in order to perform a more comprehensive analysis. The 4 most prevalent types of DR HNCs were squamous cell carcinoma (SCC), thyroid cancer, LPD, and mucoepidermoid carcinoma/acinic cell carcinoma. Similar to ordinary thyroid cancers,[65] the most prevalent cases of DR thyroid cancers were papillary carcinomas followed by follicular carcinomas. The relative frequencies of these DR cancers are in line with the results of previous studies, which reported higher prevalence for cancers of epithelial origin,[63] although these studies excluded thyroid cancers from their analyses.

While the direct cause-and-effect relationship between drug use and cancer incidence cannot be established at this time, some findings can lead us to reflect on the role of drug therapy in cancer incidence. It has been stated in the literature that radiotherapy can increase the risk of secondary cancer in the head and neck region.[66] While some patients in the included studies received radiotherapy in the head and neck

	Specific outcome	Frequency (*n*)	Relative frequency* [%]
DR cancers	squamous cell carcinoma [9,10,30,35,67–69,86,87,94]	38	36.9
	thyroid cancer [4,6,71]	27	26.2
	LPD** [5,7,77–79,81–85,88–92]	18	17.5
	mucoepidermoid carcinoma/acinic cell carcinoma [29,66,70]	10	9.7
	pharyngeal cancer [36,93]	7	6.8
	Merkel cell carcinoma [80,95]	2	1.9
	sarcomatoid carcinoma [94]	1	0.9
	total	**103**	**99.9**

region,[67–69] others did not receive it,[10,29,30,70–73] or reported that HNCs had developed regardless of receiving or not receiving radiotherapy.[6] While the genetic or acquired predisposition of individuals to secondary cancers through field cancerization,[74] immunosuppression,[75] or even infection with oncogenic viruses[76] cannot be ignored, the temporal relationship between drug use and cancer incidence, which was sometimes observed within months of its use,[30] may indeed indicate that drug use can have a significant impact on HNC development.

To explain the biological plausibility of this statement, the most prevalent drug classifications used in the included studies should be considered. The 2 most often mentioned cancer-related drug classes in these studies were immunomodulatory/immunosuppressive and chemotherapeutic drugs. These drugs may induce the double-strand breakage of the DNA structure, which may result in aberrant lesions.[77] Additionally, immunosuppression can impair immune surveillance,[75] as some chemotherapeutic drugs do.[66] However, the exact mechanisms through which drugs can cause HNCs is not yet clear.

Other, less prevalent DR HNCs reported in the literature were pharyngeal cancers, Merkel cell carcinoma and sarcomatoid carcinoma. Additional entities of DR HNCs may also be present, but they have not yet been discovered. Clinicians should be aware of the possibility of occurrence of these DR HNCs to diagnose them in a timely manner.

Site of drug-related cancers

The sites of DR HNCs closely correspond to the types of DR HNCs discussed in the previous section. These sites were the oral cavity, neck, salivary glands, including the parotid and submandibular glands, pharynx/larynx, and head/face. Clinicians should take note of the most prevalent sites of DR HNCs and implement appropriate diagnostic screening measures, such as the continuous surveillance of each site.

Limitations

Although we tried to find as many studies as possible about the subject matter, and analyze their data in a way that could be easily comprehended, this study was not without limitations. Most of the included studies about DR HNCs were case reports or cases series, which inevitably have a low level of evidence. Furthermore, some of the studies' data regarding the analyzed outcomes were incomplete. We hope that this descriptive study will help clinicians, including dentists and general practitioners, in diagnosing HNC patients. A detailed discussion on the possible intra- and extracellular pathways responsible for the development and promotion of DR cancers was well outside the scope of this study. Future research should not only be dedicated to DR HNCs, but also to DR cancers occurring within other parts of the human body.

Conclusions

In summary, drug therapy may induce secondary cancers in the head and neck region. These DR HNCs were more prevalent in older-adult populations, with no noticeable disparities between males and females after adjusting for sex-specific drugs. The most common DR HNCs were thyroid cancer, SCC, LPD, and mucoepidermoid carcinoma/acinic cell carcinoma, with the neck being the most commonly affected site. Drugs that can cause these types of cancers can be broadly classified into chemotherapeutic drugs, immunomodulatory/immunosuppressive drugs, oral contraceptives, and chemoprotective drugs. Although biologically plausible pathways may be hypothesized as the mechanisms of action of these drugs in inducing DR HNCs, the direct relationship between drug use and HNCs is yet to be established. Further research is necessary to understand the nature of DR HNCs.

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Specific outcome		Frequency (*n*)	Relative frequency* [%]
Sites of DR cancers***	oral cavity [5,9,30,69,77–79,81,82,84–92]	33	31.4
	neck [4,6,35,71,80,83]	31	29.5
	salivary glands [29,35,66,70]	18	17.1
	pharynx/larynx [7,35,36,93]	12	11.4
	head/face [10,35,67,68,83,94,95]	11	10.2
	total	105	99.6

* Note that the sum of the relative frequencies may not equal to 100% due to the rounding of numbers. ** LPD includes the following: Hodgkin and non-Hodgkin lymphomas; DLBCL; multiple myeloma; polyclonal B cell lesion; pseudolymphoma; and PSLLPI. *** Details of each site: oral cavity – lips, tongue, gingiva, palate, buccal mucosa, alveolar ridge, retromolar trigone, and sublingual; neck – thyroid gland, cervical lymph node and soft tissue; salivary glands – parotid and submandibular glands; pharynx/larynx – nasopharynx, oropharynx, hypopharynx, and larynx; head/face – scalp, frontal, zygoma, ethmoid sinus, orbital rim, maxilla, mandible, ear, eyelid, chin, nasal cavity, and pyramid.

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