Nonhormonal Drugs and Cancer

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Nonhormonal drugs probably account for only a small proportion of human cancer but have contributed many valuable insights into carcinogenic mechanisms. The antineoplastics, radiopharmaceuticals, and a few other agents account for most of the known drug-induced cancer. A number of other agents are under suspicion, usually due to studies in laboratory animals or to preliminary clinical or epidemiologic observations. This group includes some drugs in widespread use such as clofibrate and cimetidine. For a few drugs that are carcinogenic in animals, such as dapsone and isoniazid, epidemiologic studies have shown little to no evidence of carcinogenicity. Recent experimental studies have shown tumor promotion by the commonly used antidepressants amitriptyline and fluoxetine and some antihistamines, which deserve epidemiologic investigation of cancer risk. Some drugs may also protect against cancer, as suggested by the lower risk of colorectal cancer among regular users of nonsteroidal antiinflammatory drugs. Pharmacoepidemiologic studies must take into account possible confounding by the original conditions for which drugs were taken and the typically long latency period of drug-induced cancer. Improved postmarketing surveillance, continued routine case–control surveillance, and ad hoc case–control and cohort studies are needed to evaluate drugs already in use as well as newly introduced agents. — Environ Health Perspect 103(Suppl 8):191–196 (1995)

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Introduction

Drugs are given at doses sufficient to achieve a physiologic effect, but often there are acute and sometimes chronic side effects. One of the serious late consequences of certain medications, including nonhormonal agents, is the development of cancer, although these exposures contribute to only a small proportion of human cancer. This review groups nonhormonal drugs into agents classified as human carcinogens by the International Agency for Research on Cancer (IARC) (*1*); agents suspected of being human carcinogens; agents with some evidence for carcinogenicity in laboratory animals but with epidemiologic studies showing little or no carcinogenic risk in humans; and drugs that have recently come to attention because of their tumor-promoting or tumor-inhibiting abilities.

Known Human Carcinogens

Antineoplastics, radiopharmaceuticals, and a few other agents account for most of the known drug-induced cancers (Table 1) (*1*). Alkylating agents used in cancer chemotherapy are associated with subsequent development of acute nonlymphocytic leukemia and, to a lesser extent, lymphoma. Cyclophosphamide has been linked to bladder cancer (*2*), and concern has been raised generally about the long-term risk of solid tumors after using alkylating agents (*2*). IARC has classified alkylating agents, as a group, as is carcinogenic to humans, although research continues to quantify the risk for specific agents. These risks and possible substitutions by other agents must be weighed against the antineoplastic benefits.

The carcinogenic effects of drugs may be identified shortly after use, such as with chlornaphazine, a drug used more than two decades ago to treat polycythemia vera and certain cancers. Chlornaphazine was metabolized to β-naphthylamine, a potent bladder carcinogen (*3,4*). A striking incidence of bladder cancer was quickly recognized and the drug was withdrawn from use. Usually, however, more time elapses

Table 1. Nonhormonal drugs classified as human carcinogens.[a]

Class	Agent	Cancer
Analgesics and antiinflammatory agents	Mixtures containing phenacetin	Kidney, lower urinary tract
Antineoplastic agents	Chlorambucil	Leukemia
	Chlornaphazine	Bladder
	Cyclophosphamide	Bladder, leukemia
	Melphalen	Leukemia
	Myleran	Leukemia
	MOPP (and other combined chemotherapy including alkylating agents)	Leukemia, lymphoma
	Thiotepa	Leukemia
	Treosulphan	Leukemia
	Methyl-CCNU	Leukemia
Dermatologic agents	Arsenic salts	Skin
	Coal tars	Skin
	PUVA (8-methoxypsoralen and ultraviolet radiation)	Skin
Immunosuppressants	Azathioprine	Lymphoma, skin, other
	Cyclosporin A	Lymphoma, other
Radiopharmaceuticals	Radioactive phosphorus	Acute myeloid leukemia
	Radium	Osteosarcoma, nasal sinus
	Thorotrast	Liver

[a] Data from IARC (*1*).

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Abbreviations used: IARC, International Agency for Research on Cancer; NSAID, nonsteroidal antiinflammatory drugs; PUVA, methoxypsoralen plus ultraviolet radiation.

before carcinogenic effects of medications are recognized.

The other drugs known to be carcinogenic in humans include analgesic mixtures containing phenacetin, some dermatologic agents, immunosuppressants, and radiopharmaceuticals. Long-term heavy use of mixtures containing phenacetin has been linked to cancers of the renal pelvis, ureter, and bladder (*2,5–9*). This drug has been withdrawn, but the findings raise concern about the commonly used acetaminophen, which is metabolized to phenacetin. Certain dermatologic agents such as inorganic arsenic (Fowler's solution), coal tar ointments, and PUVA (8-methoxypsoralen plus ultraviolet radiation) increase the risk of skin cancer (*2,10,11*). Immunosuppressants such as azathioprine and cyclosporin A are associated with increased risk of non-Hodgkin's lymphoma, skin cancer, and certain other tumors, especially when the drugs are used with organ transplantation (*1,2*). These findings have contributed to evidence that immunosuppression by various mechanisms predisposes the development of these tumors. In addition, radiopharmaceuticals increase the risk of cancer by continuing to emit radiation when sequestered in human tissue. Thorotrast, for example, once used as a radiographic contrast medium, has been linked to certain cancers such as angiosarcoma of the liver (*12*).

Suspect Human Carcinogens

A number of other drugs are under suspicion, often because of mutagenicity or carcinogenicity in laboratory animals or occasionally because of clinical data that are insufficient to draw conclusions about the risk in humans (Table 2). Methoxyflurane and phenytoin are suspected of increasing the risk of cancer among the offspring of women who were exposed during pregnancy (*13–18*). Phenytoin use has been reported in association with lymphoma, but the risks, if any, appear small (*14–19*). Some drugs in widespread use, such as aspirin, clofibrate, cimetidine, and diuretics, are under evaluation. Aspirin has been linked to kidney cancer in some studies (*2,20*) but not all (*21*), and to non-Hodgkin's lymphoma in one recent study (*22*), while diuretics have been associated with renal-cell cancer (*23–30*). Clofibrate, a cholesterol-lowering drug, has been related to cancers of the lung, liver, and intestines (*31*), but the negative results from more recent studies have been reassuring (*2*). Cimetidine, used widely for treatment of peptic ulcer, has been related to stomach cancer (*1*), but the association may be confounded by use of the drug to treat symptoms of incipient stomach cancer. When use within 1 year of diagnosis is ignored, the association fades (*32*). It is crucial that the safety concerns over these commonly used drugs are resolved.

Table 2. Nonhormonal drugs suspected of being human carcinogens.

Class	Agent	Cancer
Anesthetics	Methoxyflurane	Wilms' tumor
Nonsteroidal antiinflammatory drugs	Aspirin	Kidney, non-Hodgkin's lymphoma
	Phenylbutazone	Leukemia
Antibacterial drugs	Chloramphenicol	Leukemia, soft tissue sarcoma
Antineoplastic agents	Bischloroethyl nitrosoureas (BCNU)	Leukemia
	Doxorubicine	Leukemia
	Mechlorethamine	Leukemia
	Prednimustine	Leukemia
	Procarbazine	Leukemia
Antifungal agents	Griseofulvin	Thyroid
	Metronidazole	Lung
Drugs for treating anemia	Iron–dextran complexes	Soft tissue sarcoma
Drugs for treating cardiovascular disorders	Clofibrate	Lung, liver, intestines
Drugs for treating CNS disorders	Phenobarbital	Lung, lymphoma
	Phenytoin	Lymphoma, neuroblastoma, soft tissue sarcoma
Drugs for treating thyroid disorders	Propylthiouracil	Breast
	Thiourea	
Drugs for treating ulcers	Cimetidine	Stomach, lymphoma

CNS, central nervous system.

The strength of the evidence for human carcinogenicity varies for the drugs in Table 2. For example, several reports indicate an association between chloramphenicol use and leukemia (*33,34*), although the risk, if any, appears small, but only one report relates chloramphenicol to soft tissue sarcoma, with some questions about the quality of the self-reported exposure data (*35*). An association between iron–dextran injections and soft tissue sarcoma is based on case reports (*36,37*), while suspicions about alum-adsorbed allergenic extracts are not supported by analysis of time trends for soft tissue sarcomas (*38*).

With more research and longer follow-up periods, some of the drugs in this group may eventually be classified as carcinogens or may be exonerated. For example, a recent report on the long-term sequelae of alkylating agents showed a 13.4-fold increased risk of acute nonlymphocytic leukemia among persons following prednimustine treatment for non-Hodgkin's lymphoma, with risks reaching about 20-fold among patients receiving higher doses (*39*). Since the drug is chemically allied to chlorambucil, which has leukemogenic properties, one could argue that the drug should now be classified as a human carcinogen based on this one study. On the other hand, several studies have shown no increased cancer risk following treatment with metronidazole (*40,41*), an antifungal medication that is both mutagenic and carcinogenic in experimental studies (*42–44*). If these results persist after additional follow-up to exclude increased risk after long latency, it would appear that metronidazole does not pose a carcinogenic risk to humans.

Drugs Evaluated with Little or No Evidence of Human Carcinogenicity

A few drugs that are mutagenic or carcinogenic in animals reveal little to no evidence of human carcinogenicity by epidemiologic studies (Table 3). Dapsone, a drug used to treat Hansen's disease (leprosy), malaria, and certain other diseases (*45*), induced mesenchymal tumors of the spleen and thyroid tumors in rats (*46–49*) and has been linked to cancer in a few case reports (*2*). Several cohort studies of patients treated for Hansen's disease, however, show no elevated risk of cancer (*50–53*).

Isoniazid, a drug used in tuberculosis treatment and prophylaxis, is mutagenic and carcinogenic, causing pulmonary tumors in mice (*2,54*). Concern over possible

Table 3. Nonhormonal drugs with studies showing some evidence of carcinogenicity in animals but with little or no evidence for human cancer risk.

Class	Agent
Antibacterial drugs	Dapsone
	Isoniazid
Psychotropic drugs	Diazepam
Drugs to treat cardiovascular disorders	Reserpine

carcinogenicity in humans was raised by the experimental data and by an epidemiologic report of an association with bladder cancer (*55–57*) and case reports of lung cancer (*59*). Several other studies, however, found no increased risk of bladder cancer (*60–63*), including a large study of approximately 3000 cases and 6000 controls (*63*). Other studies have shown no excess of lung cancer or other malignancies (*64–67*).

Reserpine, an antihypertensive medication, increases secretion of prolactin, a pituitary hormone that affects breast tissue differentiation, and induces mammary tumors in mice and rats (*2*). These findings led to an extensive evaluation of the role of reserpine in the etiology of breast cancer in women. In 1974, three studies reported associations between reserpine and breast cancer with relative risk estimates ranging from 2.0 to 3.5 (*68–70*). By 1987, IARC counted 17 case–control studies and 3 cohort studies on the relationship between reserpine and breast cancer (*2*). The relative risk estimates ranged from 0.6 to over 3, but studies with the strongest methodologies showed little or no evidence of increased risk. In a large study of approximately 1400 breast cancer cases and 1250 controls, reserpine use was associated with a nonsignificant 20% excess risk (*71*). The weight of the evidence to date suggests that reserpine has little or no effect on the risk of breast cancer. Nonetheless, a recent study suggested an excess risk among long-term users, pointing to the need for continued follow-up (*71*).

The tranquilizer diazepam enhances the growth of mammary tumors in rats (*72*) and has been suspected of increasing the risk of breast cancer and its progression (*73*). Epidemiologic studies have found no positive relation with breast cancer risk (*74–78*) or with the extent of disease and lymph node involvement (*79*), and the possibility of a protective effect has been suggested (*79*).

Promoters and Protective Agents

Some commonly used antidepressants, amitriptyline (Elavil) and fluoxetine (Prozac), and antihistamines have recently been suggested to be tumor promoters in experimental studies (Table 4). In particular, amitriptyline and fluoxetine stimulated growth of mammary fibrosarcomas in rats fed dimethylbenzanthracene (*80*). Other tricyclic analogues of amitriptyline, clomipramine and desipramine, exhibited the same properties (*81,82*). Also, several antihistamines enhanced melanoma and fibrosarcoma in mouse *in vitro* assays (*83*). Only limited epidemiologic data are available, but one cohort study involving Kaiser Permanente members showed no excess cancer among amitriptyline users (*84*). Further epidemiologic evaluation is needed, given the widespread use of these drugs.

Some drugs may protect against cancer, as suggested by the lower risk of colorectal cancer and polyps among regular users of nonsteroidal antiinflammatory drugs (NSAID) (*85–96*). Experimental studies have shown inhibition of colorectal cancer and adenomas (*97–100*), possibly due to inhibition of the enzyme cyclooxygenase, which controls synthesis of prostaglandins that may increase cell proliferation and tumor growth (*101–104*). Case–reports (*105–107*) and two randomized trials (*86,87*) suggested that the NSAID sulindac caused reduction of the number and size of colorectal polyps in patients with familial adenomatous polyposis. Case–control and cohort studies, with few exceptions, have consistently shown regular use of NSAIDs to be associated with an approximately 50 to 60% reduction of colorectal cancer (*88–96,108*). More information is needed on the dose and frequency of use that might confer protection. The Physicians Health study did not show any protection with regular aspirin use (*109*), but the dose may have been too low or follow-up too short (*110*). The ongoing Women's Health Study, a randomized trial of 100 mg aspirin every other day among 40,000 female health professionals, will have longer follow-up and may clarify whether low-dose aspirin decreases colorectal cancer incidence (*111*). Other trials are in progress to evaluate the effect of NSAIDs on polyp development in high-risk groups such as patients with familial polyposis or with a past history of adenomatous polyps (*110,112*).

It has been suggested that cimetidine, suspected of increasing stomach cancer risk, may protect against prostate cancer (*113*). Cimetidine and other histamine$_2$ receptor antagonists may inhibit the binding of dihyrotestosterone to androgen receptors and lead to increased serum estradiol (*113*). A Danish cohort study of cimetidine users reported no excess of stomach cancer but less than expected prostate cancer incidence after 4 years or more of use (*114*). Confirmation is needed to determine if an opportunity exists for chemoprevention of prostate cancer, the most common malignancy among men.

Conclusion

Identifying carcinogenic drugs is difficult because of the typically long latent period of cancer, the inability to distinguish drug-induced cancers from those induced by other agents, possible confounding by the condition for which drugs were taken, the widespread and even casual use of some drugs, and the general lack of epidemiologic surveillance for drug-induced cancer. Animal and microbial screening tests for mutagenicity and carcinogenicity must continue and can help set priorities for epidemiologic research, but they must be interpreted cautiously, particularly with reference to dose extrapolations. The Food and Drug Administration should be given legal authority to require postmarketing surveillance as part of the approval process for new drugs. Epidemiologic research should incorporate routine surveillance through record linkage surveys and case–control studies such as those pioneered by the Kaiser prepaid health plan and the Sloan Epidemiology Unit at Boston University. Further ad hoc case–control and cohort studies (with extended follow-up) are needed to help settle a number of hypotheses about drug-related cancer, and also to provide better understanding of carcinogenic mechanisms. Minimizing or eliminating the use of harmful drugs and searching for alternatives may prevent some, albeit a relatively small proportion, of human cancer.

Table 4. Nonhormonal drugs and cancer: possible promoters and protective agents.

Drug types	Agent	Action
Promoters		
Antidepressants	Amitriptyline (Elavil)	Promotes fibrosarcomas in mice and mammary tumors in rats
	Flouxetine (Prozac)	
Antihistamines	Astemizole	Promotes melanoma and fibrosarcomas in mice
	Loratidine	
	Hydroxyzine	Promotes melanoma in mice
Protective agents		
Nonsteroidal antiinflammatory drugs	Aspirin	Reduces risk of colorectal polyps and cancer in humans
	Piroxicam	
	Sulindac	
Drugs for treating ulcers	Cimetidine	Reduces risk of prostate cancer

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