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Short Note

Incidence of Breast, Prostate, Testicular and Thyroid Cancer in Italian Contaminated Sites with Presence of Substances with Endocrine Disrupting Properties

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Abstract: The aim of the present study was to investigate the incidence of breast (females), prostate, testicular and thyroid cancer in the Italian National Priority Contaminated Sites (NPCSs), served by cancer registries, where the presence of endocrine disruptors (EDs), reported to be linked to these tumors, was documented. Evidence of carcinogenicity of EDs present in NPCs was assessed based on evaluation by international scientific institutions/committees. Standardized Incidence Ratios (SIRs) were computed for each NPCS and cancer site with reference to the time window 1996-2005. Excess incidence of one or more cancer site at study was found in twelve out of fourteen NPCSs. Significantly increased SIRs were found for breast cancer in eight NPCSs, for prostate cancer in six, for thyroid cancer (both gender) in four and for testicular cancer in two. Non significantly increased SIRs were found in five NPCSs for testicular cancer and in two for thyroid cancer (males). Even if increased incidence of one or more cancer sites at study were found in several NPCSs, the ecological study design and the multifactorial etiology of the considered tumors do not allow reaching conclusions in terms of causal links with environmental contamination. In light of the observation of some excesses in SIRs, continuing epidemiological surveillance is warranted.

Keywords: cancer; incidence; endocrine disruptors; environmental exposure

1. Introduction

Over the past decade, in industrialized countries served by cancer registries, an increased incidence of breast, prostate, testicular and thyroid cancer has been observed. The increase in incidence of endocrine-related cancers in humans cannot be explained solely in terms of genetics, better diagnosis or life style. Currently, it is believed that the increase may be partially related to exposure to environmental chemicals, some of which with endocrine disrupting properties [**1**].

An endocrine disruptor (ED) is commonly defined as an exogenous substance or mixture that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones, and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)population [**1-2**]. Similar to hormones, EDs can act at low dose, may have non-monotonic dose responses, will have tissue specific and time effects, will show different effects and dose responses during development relative to adults, and will likely not have a threshold [**3**].

A large number of chemicals have been identified as endocrine disruptors and humans can be exposed to them either due to their occupation and/or through dietary and environmental exposure [**4**]. Among the environmental pollutants, the best-characterized chemicals with endocrine disrupting properties considered to be involved in cancer etiology include dioxins, dioxin-like compounds, furans, polychlorinated biphenyls (PCBs), solvents, heavy metals, dichlorodiphenyltrichloroethane (DDT) and its metabolite dichorodiphenyldichloroethylene (DDE),

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and some other pesticides **[5-6].** By far the most research into associations between EDs and tumors has been carried out with breast, prostate and testicular cancer **[7-19],** while thyroid cancer has received very little attention. Because of concerns associated with the increase of endocrine-related cancers, several International Scientific Organizations and/or International Scientific Advisory Committees have included among the priorities the need to implement epidemiological studies, to integrate epidemiological data with data on the environment, the food chain and human biomonitoring data, and to strengthen the studies of chemical mixtures exposure **[20].**

The aim of the present study was to investigate the incidence of breast, prostate, testicular and thyroid cancer in the Italian National Priority Contaminated Sites (NPCSs), served by cancer registries, included in the SENTIERI epidemiological surveillance programme **[21**]) where the presence of EDs reported to be linked to these tumors were reported. The Italian NPCSs are characterized by the presence of major industrial activities (e.g. refineries, petrochemical and metallurgic plants), and industrial and uncontrolled waste sites. In these NPCSs several environmental pollutants, are present, some of which with recognized or suspected endocrine disrupting properties.

Thyroid cancer was included even if the current understanding of its etiology does not clearly link it to an endocrine mechanism. Still some experimental and epidemiological studies have suggested that estrogen may play an important role in the development and progression of papillary thyroid cancer; this might make it plausible that xenoestrogens, such as cadmium or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), might also contribute to the risk [**22-23**].

2. Materials and Methods

This is an exploratory ecological study. Cancer incidence (all ages) was investigated for breast (females), prostate, testis and thyroid, based on figures produced by the Italian Association of Cancer Registries (AIRTum), within SENTIERI Project - the Italian epidemiological surveillance system for population resident in NPCs, as discussed elsewhere **[24]**. Evidence of carcinogenicity of EDs for the tumours at study was assessed based on evaluation by International Scientific Organizations and International Scientific Advisory Committees; we took into consideration only the EDs that could be identified as environmental pollutants in the study areas. Relevant papers were identified from five major sources: International Agency for Research on Cancer (2015), Word Health Organization/United Nation Environment Programme (2013), Europen Commission (2012), European Environment Agency (2012), The Endocrine Society (2015) [**1, 25-28]**. This was considered an accurate account of the state of science on the potential human carcinogenic health effects of environmental exposure to EDs up to a year prior to their publication. In order to update such evidence, relevant literature published in the last four years has also been reviewed. This literature search was carried out in PubMed. Moreover, a search was carried out on available environmental data to ascertain the presence of EDs in the NPCSs at study. The environmental data were collected through the sources of the Italian Ministry of Environment, the legislative national decrees where the NCS are defined, the local environmental agencies [**29-30**]. The available data are related to the presence of the substances in the various environmental matrices, not necessarily to their concentrations**.** The existence of human biomonitoring data (blood, serum and milk) reporting high level of substances with endocrine disrupting properties and other monitoring data (food, plants) regarding the NPCSs at study was verified by a search in PubMed **[31-44].**

Age, gender, socio-economic-deprivation-index adjusted Standardized Incidence Ratios (SIRs), with their 90% confidence interval, were computed for each CS and cancer site by the Italian Association of Cancer Registries **[24]**, with reference to the time window 1996-2005. Reference rates were derived from the pool of the cancer registries from Northern-Central Italy or from Southern-Central Italy, depending on the study area localization.

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3. Results

The NPCSs served by a Cancer Registry were seventeen. Three NPCSs were excluded from the study as the presence of EDs could be reasonably excluded. Therefore, the NPCSs finally included in the study were fourteen.

The environmental pollutants with suspected or recognized endocrine disrupting properties reported to be carcinogenic for the tumors at study by the five international scientific institutions/committees listed above are shown in table 1. Information on the characterization of the NPCSs with respect to the presence of major sources of pollution is reported in table 2, together with the indication of the EDs of interest detected in the environmental matrices, human biomonitoring data, and food monitoring data. The age, gender, socio-economic-deprivation-index adjusted SIRs, with their 90% confidence intervals (90%CI), are reported in table 3. Excess incidence of one or more cancer site at study was found in twelve out of fourteen NPCSs. Significantly increased SIRs were found for breast cancer in eight CSs, for prostate cancer in six, for thyroid cancer (both gender) in four and for testicular cancer in two. Furthermore, not significantly increased SIRs were found in five CSs for testicular cancer and in two for thyroid cancer (males).

Table 1. Environmental pollutants with endocrine disrupting properties considered to be carcinogenic for the tumors at study by scientific institutions/advisory committees

Cancer site	**IARC** [1]	**WHO/UNEP** [25]	**European Commission** [26]	**European Environmental Agency** [27]	**The Endocrine Society** [28]
Breast	PCB Ethylene oxide	Dioxins Furans PCBs Solvents	Cadmium Solvents	Oestrogenic EDs	Dioxins
Prostate	Arsenic Cadmium Rubber production industry	Arsenic Cadmium PCBs Pesticides	Arsenic Cadmium PCBs Pesticides	Pesticides	Cadmium Farming PCBs
Testis		Prenatal exposure to POPs Fungicides PBDE Pesticides	Organochlorine chemicals (including DDT and some pesticides) PCBs	DDE DDT PCBs	Arsenic Cadmium PCBs
Thyroid		Pesticides TCDD	PCBs Pesticides Solvents	PCBs	

Abbreviations: DDE= Dichorodiphenyldichloroethylene; DDT= Dichlorodiphenyltrichloroethane; PBDE= Polybrominated Diphenyl Ethers; IARC= International Agency for the Research on Cancer; PCBs=Polychlorinated Biphenyls; POPs=Persistent organic pollutants; TCDD=2,3,7,8-Tetrachlorodibenzo-p-dioxin; WHO/UNEP= World Health Organization/United Nations Environment Programme

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Table 2. National Priority Contaminated sites (NPCSs) information on pollution sources, and endocrine disruptors (EDs) of interest detected in environmental matrices, human biological samples, and food

National Priority Contaminated Site (NPCS)	Area description		Other data on EDs of interest	
	Pollution sources	EDs of interest detected in environmental matrices	Human biomonitoring	Food
Bacino Chienti	Shoe factories	PCDDs/PCDFs, benzene, toluene, other solvents		
Brescia Caffaro	Chemical plants, landfill	As, PCBs, PCDDs/PCDFs, chlorobenzene	PCDDs/PCDFs, PCB (human serum)	PCB (food of animal and vegetal origin); PCDDs/PCDFs, PCB (cattle's meat, cow milk, forage)
Fidenza	Chemical plants, urban and hazardous waste landfills	As, PCBs, PCDDs, benzene, other solvents		
Litorale Domizio Flegreo	Urban waste landfill, illegal dumping sites, illegal burning of waste	As, PCBs, PCDDs, benzene, other solvents	PCDDs/PCDFs (breast milk)	PCDDs/PCDFs, (cow and buffalo's milk)
Laguna Grado Marano	Cellulose production plant, dockyard	As, PCDDs, benzene, other solvents		
Laghi Mantova	Metallurgy plants, paper plant, petrochemical plant, harbor area, industrial waste landfills, hazardous waste incinerator	AS, Cd, PCDDs, ethylbenzene, other solvents		PCBs (fruit,vegetables)
Milazzo	Oil refinery, steel plant, thermal power plant, electrical equipment factories, illegal dumping site	PCDDs, heavy metals. Benzo(a)pyrene	Cd, As (serum)	
Porto Torres	Chemical plants, petrochemical plant, refinery, power plant, harbor area, illegal dumping site	As, Cd, chlorobenzene, other solvents		PCDDs (fish and other seafood)
Priolo	Chemical plants, petrochemical plant, refinery, harbor area, hazardous waste landfills	PCB, hexachlorobenzene	Dioxins, PCB, HCB (breast milk and puerperal hair)	Cd, Pb, Hg, PCDDs, organochlorine compounds (fish and other seafood)
Sassuolo-Scandiano	Ceramic industries, industrial waste landfills	Heavy metals		
Taranto	Oil refinery, steel plant,	As, Cd, PCDDs, PCBs,	As, Cd in serum and	PCDDs, PCB (sheep and

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	harbor area, cement plant, controlled and illegal waste dumps	benzene, xylene	urine; PCDDs, PCBs (serum and milk)	cow's milk, clams); PCB, HCB, PAHs (clams)
Terni-Papigno	Steel plant, hazardous waste landfills	PCB		
Trento Nord	Chemical plant	Solvents		
Venezia (P. Marghera)	Chemical plants, petrochemical plant, oil refinery, harbor area, illegal dumping sites	As, Cd, PCBs, PCDDs, solvents		As, Cd, PCDDs, PCDFs (shellfish)

Abbreviations: As=Arsenic; Cd=Cadmium; CSs= Contaminated sites; BPA= Bisphenol A; EDs= endocrine disruptors HCB=Hexachlorobenzene; PAHs=Polycyclic Aromatic Hydrocarbons; PBDE= Polybrominated Diphenyl Ethers; PCBs=Polychlorinated Biphenyls; PCDDs=Polychlorinated dibenzo-p-dioxins; PCDFs=Polychlorinated dibenzofurans; POPs= Persistent organic pollutants; SIR=Standardized Incidence Ratio; TCDD=2,3,7,8-Tetrachlorodibenzo-p-dioxin

Table 3. Standardized Incidence Ratios (SIRs) with 90% Confidence intervals (CI), 1996-2005

National Priority Contaminated Site (NPCS)	Thyroid Cancer				Testicular Cancer		Prostate Cancer		Breast Cancer	
	Males		Females						Females	
	obs	SIR* (CI 90%)	obs	SIR* (CI 90%)	obs	SIR* (CI 90%)	obs	SIR* (CI 90%)	obs	SIR* (CI 90%)
Basso Bacino Fiume Chienti	6	83 (36-163)	21	85 (57-122)	11	148 (83-245)	181	120 (106-136)	227	117 (104-130)
Brescia Caffaro	47	170 (132-217)	131	156 (134-180)	31	102 (74-137)	807	124 (117-132)	1187	125 (120-132)
Fidenza	18	145 (94-215)	32	88 (64-118)	15	134 (83-207)	339	105 (96-115)	403	102 (94-111)
Litorale Domizio Flegreo and Agro Aversano	54	95 (75-119)	147	69 (60-79)	70	108 (87-131)	404	76 (70-83)	1097	103 (98-108)
Laguna Grado Marano	3	33 (9-86)	15	57 (35-88)	15	176 (109-272)	216	107 (96-120)	249	95 (85-106)
Laghi Mantova	21	174 (117-251)	58	155 (123-193)	17	141 (90-211)	315	103 (94-114)	472	113 (105-122)
Milazzo	6	124 (54-245)	24	140 (96-196)	4	98 (34-225)	54	99 (78-125)	80	108 (89-130)
Porto Torres	30	69 (50-94)	155	97 (84-111)	51	135 (105-170)	601	137 (128-147)	966	125 (119-132)

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Priolo	34	89 (66-119)	132	94 (81-109)	37	103 (77-136)	417	105 (96-114)	712	111 (104-118)
Sassuolo Scandiano	41	146 (111-190)	106	130 (110-152)	39	121 (91-159)	540	92 (86-99)	702	90 (85-96)
Taranto	34	158 (116-210)	98	120 (101-142)	20	108 (72-158)	303	130 (118-143)	497	145 (134-156)
Terni Papigno	32	106 (77-142)	67	66 (53-81)	32	121 (88-163)	577	89 (83-95)	902	114 (107-120)
Trento Nord	20	71 (47-103)	71	70 (57-85)	32	104 (76-140)	527	88 (82-94)	876	98 (92-103)
Venezia Porto Marghera	57	74 (59-92)	165	71 (62-81)	76	94 (77-114)	2075	103 (100-107)	3045	110 (107-114)

* adjusted for age and socio-economic deprivation index

Abrbreviation: obs=observed cases

4. Discussion

An excess in incidence was mainly found in several NPCs for breast and prostate cancers, which are relatively common tumors. The rarity of testicular and thyroid cancers, and the small number of cases on which the findings were based, might explain the lower number of significant excesses Additional research should take into account the peculiarity of each of these tumors (different window of vulnerability, peak incidence, reported shift of the age of onset and/or increase of specific histotypes, as for thyroid cancer). Due to the rarity of testicular and thyroid cancer, an extension of the length of study window is indicated.

5. Conclusions

In conclusion, even if increased incidence of one or more cancer sites at study was found in several NPCSs, the ecological study design and the multifactorial etiology of the considered tumors do not allow reaching conclusions in terms of causal links with environmental contamination. However, the observed increase encourage to perform studies with an analytical epidemiological approach. Moreover, in light of the observation of some excesses in SIRs, endocrine disruptors reported to be carcinogenic should be considered as a priority in environmental clean-up, as recommended by several scientific institutions and/or advisory committees **[2,20,45-46].** Meanwhile, in the contaminated sites, a continuing epidemiological surveillance is warranted, and an exposure assessment that include the detection of further contaminants with ED properties, also emerging (e.g. PFAS, steroidal estrogens), is recommended.

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The following abbreviations are used in this manuscript:

AS	Arsenic
Cd	Cadmium
CI	Confidence Interval
CSs	Contaminated Sites
DDE	Dichorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
EDs	Endocrine disruptors
IARC	International Agency for Research on cancer
HCB	Hexachlorobenzene
NPCSs	National Priority Contaminated Sites
PAHs	Polycyclic Aromatic Hydrocarbons
PBDE	Polybrominated Diphenyl Ethers
PCBs	Polychlorinated Biphenyls
PCDDs	Polychlorinated Dibenzo-p-dioxins
PCDFs	Polychlorinated Dibenzofurans
POPs	Persistent Organic Pollutants
SIR	Standardized Incidence Ratio
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
UNEP	United Nations Environment Programme
WHO	World Health Organization

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Authors' contribution

MB conceived the whole study, and drafted the manuscript. AZ contributed to reviewing the study design and the manuscript. EB contributed to collecting environmental data. MC contribute to collecting environmental data and commenting the manuscript. PC helped in designing the study and edited the manuscript in the final form. All authors read and approved the version submitted.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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