Communication

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 tumours, was documented. Evidence of carcinogenicity of EDs present in NPCSs was assessed based on evaluation by international scientific institutions and committees. Standardized Incidence Ratios (SIRs) were computed for each NPCS and cancer site between 1996 and 2005. Excess incidence of one or more cancer site studied 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). In a small number of instances a significant deficit was reported, mainly for thyroid and prostate cancer. Although increased incidence of one or more cancer sites studied were found in several NPCSs, the ecological study design and the multifactorial aetiology of the considered tumours do not permit concluding causal links with environmental contamination. Regarding 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 [1,2]. 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 environmental chemical exposure, some of which have endocrine disrupting properties [2].

An endocrine disruptor (ED) is commonly defined as an exogenous substance or mixture that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones, and which consequently causes adverse health effects in an intact organism, or its progeny, or (sub)population [2,3]. Like 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 are likely not to have a threshold [4].

Many chemicals have been identified as endocrine disruptors, and humans can be exposed to them either due to their occupation, through dietary and environmental exposure, or both [5]. Among environmental pollutants, the best-characterized chemicals with endocrine disrupting properties considered to be involved in cancer aetiology include dioxins, dioxin-like compounds, furans,
polychlorinated biphenyls (PCBs), solvents, heavy metals, dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), as well as other pesticides [6,7].

By far the most studies relating to the association between EDs and tumours have been carried out for breast, prostate, and testicular cancer [8–20], while thyroid cancer has received very little attention. Because of concerns associated with the increase of endocrine-related cancers, several international scientific organizations and advisory committees have included among their priorities the need to implement epidemiological studies to integrate epidemiological data with data on the environment, food chain, and human biomonitoring data, and to strengthen studies on chemical mixtures exposure [21].

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, where the presence of EDs linked to these tumours was reported. The study was part of the Italian Epidemiological Study of Residents in National Contaminated Sites (SENTIERI Project) [22].

The Italian NPCSs are characterized by the presence of major industrial activities (refineries, petrochemical, and metallurgic plants), and industrial and uncontrolled waste sites. In these NPCSs, several environmental pollutants, some of which have recognized or suspected endocrine disrupting properties, were detected. PCBs, dioxins, heavy metals, and solvents represent the principal sources of pollution in these areas; in most of the NPCSs they occur in the form of mixtures. Combinations of EDs can produce a significant effect, even when each chemical is present at a low dose that individually does not induce observable effects [23,24].

Thyroid cancer was included even if the current understanding of its aetiology does not clearly link it to an endocrine mechanism. Still, some experimental and epidemiological studies have suggested that oestrogen 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), may also contribute to the risk [25,26].

It is worth noting that the aetiological role of EDs and other chemicals in the pathogenesis of endocrine tumours is still a matter of manifold research activities, and the mechanisms through which chemicals may induce these tumours are not completely understood. At present, researchers have mainly focused their attention on the disrupting properties of chemicals related to the pathogenesis of endocrine tumours. However, other mechanisms, such as oxidative stress and DNA damage, may potentially contribute to the carcinogenesis of endocrine tumours. For example, many heavy metals, dioxins, PCBs, polycyclic aromatic hydrocarbons (PAHs), and other carcinogens have been shown to cause oxidative stress [27–29]. Nevertheless, according to Silisin and Högberg [30], “oxidative stress sometimes can be an important causative factor, but sometimes only a bystander in an agent’s, or a mixture’s, toxicological profile”. Moreover, some EDs could act through an indirect mechanism, as is the case of breast cancer. For this tumour, several studies suggest that the bioaccumulation of some persistent organic pollutants (PCBs and TCDD) in adipose tissue promotes the development of obesity and ultimately either influences development or progression of breast cancer, or both [31].

2. Materials and Methods

This is an exploratory ecological study. Cancer incidence (all ages) was investigated for breasts (females), prostate, testis, and thyroid, based on figures produced by the Italian Association of Cancer Registries (AIRTum), within the SENTIERI Project [22], as discussed elsewhere [32]. Evidence of carcinogenicity of EDs for the tumours included in the study was assessed based on evaluations carried out by international scientific organizations and 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: World Health Organization/United Nation Environment Programme (2013), International Agency for Research on Cancer (2015), European Commission (2012), European Environment Agency (2012), and The Endocrine Society (2015) [2,33–36]. 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. To update such evidence, relevant literature published in the last four years has also been reviewed. This literature search was carried out in PubMed. In addition, a search was carried out on available environmental data to ascertain the presence of EDs in the NPCSs in the study. The environmental data were collected from the Italian Ministry of Environment, from the legislative national decrees where the NPCSs are defined, and from local environmental agencies [37,38]. 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 levels of endocrine disrupting chemicals and other monitoring data (food and plants) regarding the NPCSs was verified by a search in PubMed [39–52].

Age, gender, and socio-economic-deprivation-index adjusted Standardized Incidence Ratios (SIRs), with their 90% confidence intervals, were computed for each NPCS and cancer site by the Italian Association of Cancer Registries [32], referring to the 1996–2005 time window. Reference rates were derived from the pool of cancer registries from Northern-Central Italy or from Southern-Central Italy, depending on the study area localization.

3. Results

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

The environmental pollutants with suspected or recognized endocrine disrupting properties reported to be carcinogenic for the tumours studied by the five abovementioned international scientific institutions/committees 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% CIs), are reported in Table 3. Excess incidence of one or more cancer sites studied was found in twelve out of the fourteen NPCSs. Significantly increased SIRs were found for breast cancer in eight NPCSs, for prostate cancer in six NPCSs, for thyroid cancer (both genders) in four NPCSs, and for testicular cancer in two NPCSs. Furthermore, non-significant increases in SIRs were found in five NPCSs for testicular cancer and in two for thyroid cancer (males). Significant SIRs deficits were also found: for thyroid cancer in four NPCSs (in one NPCS in both genders, in three NPCSs only in women), for testicular cancer in three NPCSs, and for breast cancer in one NPCS.
Table 1. Environmental pollutants with endocrine disrupting properties considered to be carcinogenic by scientific institutions/advisory committees for the tumours studied.

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

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.
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.

| NPCS                  | Area Description                                                   | Pollution Sources                                                                 | EDs of Interest Detected in Environmental Matrices | Human Biomonitoring                      | Food                                                                 |
|-----------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------|------------------------------------------|----------------------------------------------------------------------|
| Bacino Chienti        | Shoe factories                                                      | PCDDs/PCDFs, benzene, toluene, other solvents                                   |                                                  |                                          | PCB (food of animal and vegetal origin); PCDDs/PCDFs, PCB (cattle’s meat, cow milk, forage) |
| Brescia Caffaro       | Chemical plants, landfill                                           | As, PCBs, PCDDs/PCDFs, chlorobenzene                                            | PCDDs/PCDFs, PCB (human serum)                  |                                          | PCB, PCBs, PCDDs, PCB (human serum)                                    |
| Fidenza               | Chemical plants, urban and hazardous waste landfills                | As, PCBs, PCDDs, benzene, other solvents                                        |                                                  |                                          | PCB (food of animal and vegetal origin); PCDDs/PCDFs, PCB (cattle’s meat, cow milk, forage) |
| 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 (cattle’s meat, cow milk, forage) |
| Laguna Grado Marano   | Cellulose production plant, dockyard                               | As, PCDDs, benzene, other solvents                                              |                                                  |                                          | PCB (food of animal and vegetal origin); PCDDs/PCDFs, PCB (cattle’s meat, cow milk, forage) |
| Laghi Mantova         | Metallurgy plants, paper plant, petrochemical plant, harbour 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. Benz(a)pyrene                                               | Cd, As (serum)                                  |                                          | PCBs (fruit, vegetables)                                               |
| Porto Torres          | Chemical plants, petrochemical plant, refinery, power plant, harbour area, illegal dumping site | As, Cd, chlorobenzene, other solvents                                            | PCDDs (fish and other seafood)                  |                                          | PCBs (fruit, vegetables)                                               |
| Priolo                | Chemical plants, petrochemical plant, refinery, harbour area, hazardous waste landfills | PCB, hexachlorobenzene                                                          | Dioxins, PCB, HCB (breast milk, and puerperal hair) |                                          | PCBs (fruit, vegetables)                                               |
| Sassuolo-Scandiano    | Ceramic industries, industrial waste landfills                     | Heavy metals                                                                      |                                                  |                                          | PCBs (fruit, vegetables)                                               |
| Taranto               | Oil refinery, steel plant, harbour area, cement plant, controlled and illegal waste dumps | As, Cd, PCDDs, PCBs, benzene, xylene                                              | As, Cd (serum and urine); PCDDs/PCDFs, PCBs (serum and milk) |                                          | PCBs (fruit, vegetables)                                               |
| Terni-Papigno         | Steel plant, hazardous waste landfills                              | PCB                                                                               |                                                  |                                          | PCBs (fruit, vegetables)                                               |
| Trento Nord           | Chemical plant                                                      | Solvents                                                                          |                                                  |                                          | PCB (fruit, vegetables)                                               |
| Venezia Porto Marghera| Chemical plants, petrochemical plant, oil refinery, harbour area, illegal dumping sites | As, Cd, PCBs, PCDDs, solvents                                                    |                                                  |                                          | PCBs (fruit, vegetables)                                               |

NPCS: National Priority Contaminated site; As: Arsenic; Cd: Cadmium; EDs: Endocrine disruptors HCB: Hexachlorobenzene; PAHs: Polycyclic Aromatic Hydrocarbons; PCDDs: Polychlorinated dibenzo-p-dioxins; PCDFs: Polychlorinated dibenzofurans.
Table 3. Standardized Incidence Ratios (SIRs) with 90% confidence intervals (CIs), 1996–2005.

| NPCS (Geographical Area)                                      | Thyroid Cancer | Testicular Cancer | Prostate Cancer | Breast Cancer |
|---------------------------------------------------------------|----------------|------------------|-----------------|--------------|
|                                                               | Males          | Females          | Males           | Females      | Males          | Females          | Males           | Females      | Males           | Females          | Males           | Females          |
| Basso Bacino Fiume Chienti (Central Italy)                    | 6              | 21               | 11              | 181           | 227           | 117             | 104–130         |               |               | 117             | 104–130         |               |
| Brescia Caffaro (Northern Italy)                              | 47             | 131              | 31              | 807           | 1187          | 125             | 120–132         |               |               | 125             | 120–132         |               |
| Fidenza (Northern Italy)                                     | 18             | 32               | 15              | 339           | 403           | 102             | 94–111          |               |               | 102             | 94–111          |               |
| Litorale Domizio Flegreo and Agro Aversano (Southern Italy)  | 54             | 147              | 70              | 404           | 1097          | 103             | 98–108          |               |               | 103             | 98–108          |               |
| Lago Grado Marano (Northern Italy)                           | 3              | 15               | 15              | 216           | 249           | 95              | 85–106          |               |               | 95              | 85–106          |               |
| Laghi Mantova (Northern Italy)                               | 21             | 58               | 17              | 315           | 472           | 113             | 105–122         |               |               | 113             | 105–122         |               |
| Milazzo (Southern Italy)                                     | 6              | 24               | 4               | 54            | 80            | 108             | 89–130          |               |               | 89              | 89–130          |               |
| Porto Torres (Southern Italy)                                | 30             | 155              | 51              | 601           | 966           | 125             | 119–132         |               |               | 125             | 119–132         |               |
| Priolo (Southern Italy)                                      | 34             | 132              | 37              | 417           | 712           | 111             | 104–118         |               |               | 111             | 104–118         |               |
| Sassuolo Scandiano (Northern Italy)                          | 41             | 106              | 39              | 540           | 702           | 90              | 85–96           |               |               | 90              | 85–96           |               |
| Taranto (Southern Italy)                                     | 34             | 158              | 20              | 303           | 497           | 145             | 134–156         |               |               | 145             | 134–156         |               |
| Terni Papigno (Central Italy)                                | 32             | 67               | 32              | 577           | 902           | 114             | 107–120         |               |               | 114             | 107–120         |               |
| Trento Nord (Northern Italy)                                 | 20             | 71               | 32              | 527           | 876           | 98              | 92–103          |               |               | 98              | 92–103          |               |
| Venezia Porto Marghera (Northern Italy)                      | 57             | 165              | 76              | 2075          | 3045          | 110             | 107–114         |               |               | 110             | 107–114         |               |

*: adjusted for age and socio-economic deprivation index; Abbreviation: obs.: observed cases.
4. Discussion

A statistically significant excess in incidence occurred in twenty-two circumstances concerning twelve NPCSs, mainly for breast and prostate cancers, which are relatively common tumours. The low number of testicular and thyroid cancer excesses may be explained by the sparse number of cases on which the findings were based. In a smaller number of instances (eleven circumstances concerning six NPCSs) a significant deficit was reported, mainly for thyroid and prostate cancer. Excesses were altogether more frequent than deficits. These findings are suggestive of an overall adverse effect associated with residence in NPCSs, even if a role of random variability, confounding and alternative explanations cannot be ruled out, due to the adoption of an ecological study design.

Additional research should consider the peculiarity of each of these tumours (different window of vulnerability, peak incidence, reported shift of the age of onset, and increase of specific histotypes). Due to the rarity of testicular and thyroid cancer, an extension of the length of study window is indicated.

5. Conclusions

Due to the ecological approach of the study, we could not adjust for several confounding factors reported to be risk factors or sources of exposure for the tumours studied (smoking, alcohol consumption, obesity, genetic predisposition, use of personal care products, and use of pharmaceutical drugs) [1,2]. Thus, even if an increased incidence of one or more cancer sites studied was found in several NPCSs, the study design and the multifactorial aetiology of the considered tumours do not permit conclusions to be formed in terms of causal links with environmental contamination. Moreover, the complexity of exposures to multiple chemicals with suspected endocrine disrupting properties, and the possibility of other potential mechanisms of their action (oxidative stress, or DNA damage) [27–29], make it difficult to hypothesize on substances and mechanisms that have determined the excesses of tumours in some NPCSs.

However, the observed increases encourage further analytical epidemiological studies to be performed. Due to the observation of some excesses in SIRs, chemicals reported or suspected to be carcinogenic for the tumours studied should be a priority in environmental clean-up, even if they do not act through endocrine-disrupting mechanisms [2,21,53,54]. Furthermore, a continuing epidemiological surveillance is warranted in the NPCSs. An exposure assessment that includes the detection of further emerging contaminants with endocrine disrupting properties, such as perfluoroalkyl substances (PFAS), is also recommended.

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Abbreviations
The following abbreviations are used in this manuscript:

- As: Arsenic
- Cd: Cadmium
- CI: Confidence Interval
- DDE: Dichlorodiphenyldichloroethylene
- DDT: Dichlorodiphenyltrichloroethane
- EDs: Endocrine disruptors
- IARC: International Agency for Research on cancer
- HCB: Hexachlorobenzene
- NPCs: National Priority Contaminated Sites
- PAHs: Polycyclic Aromatic Hydrocarbons
- PBDE: Polybrominated Diphenyl Ethers
- PCBs: Polychlorinated Biphenyls
- PCDDs: Polychlorinated Dibenzo-p-dioxins
- PCDFs: Polychlorinated Dibenzofurans
- PFAS: Perfluoroalkyl substances
- 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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