# A comparison of the cancer-related mortality of France and Italy using the multiple cause-of-death approach

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Multiple cause-of-death data (MCOD) are increasingly used in order to 1) re-evaluate mortality levels attributed to a given condition, 2) to examine what are the most frequent/specific associations of causes involving this condition. We use this approach to analyse and compare cancer-related mortality of Italy and France. Among all causes of death, cancer ranks first in France and second in Italy. Though treatments have improved, cancer remains a very lethal disease. Thus it is expected that cancer often is selected as the underlying cause of the death (UCD). In a previous study (Désesquelles et al 2010), we have shown that in both countries, mentions as UCD represent half of the mentions of a neoplasm on death certificates. It is much lower than for other less life-threatening diseases (e.g. for endocrine, nutritional and metabolic diseases, the same indicator is equal to one fourth), but it may vary according to anatomic sites. Neoplasms with the best survival profiles may be considered as chronic conditions, and the presence of comorbid conditions among long-term cancer survivors is likely to become more frequent. We believe that all these elements justify the interest of using the MCOD approach to specifically study cancer-related mortality.

**Data and indicators**

Data for the two countries are for year 2003. They are based on the information reported on the death certificates by the certifying physicians and coded according to the 10$^{th}$ International classification of diseases (ICD-10). The list of causes we use comprises 15 large groups and 69 sub-groups[1]. We first calculate age- and sex-standardized mortality rates for 1) a given cause reported as the UCD, 2) the same cause reported as multiple (underlying or contributing) cause of the death. The **Standardized Ratio of Multiple to Underlying cause** (SRMU) is defined as the ratio of the second to the first of these two rates. It measures the underestimation of the role played by a given condition in overall mortality when the analysis is performed using the underlying cause only.

We developed an indicator of the frequency of the combinations of causes that can be used to compare various underlying causes within a country, or various countries for a given underlying cause (Désesquelles et al, 2010). The **Cause-of-Death Association Indicator** (CDAI) is the ratio between:

- the standardized prevalence at death of a combination between a contributingcause *c* and an underlying cause *u* among all deaths assigned to that underlying cause ($SP_{c/u}$);
- the standardized prevalence at death of the same contributing cause among all deaths ($SP_c$). It represents the prevalence that would be observed for underlying cause *u* and contributing cause *c* if these two causes were independent.

[1] See the list of the groups in the appendix.

Standardization is performed in order to remove the effect of the varying age structure of deaths according to the underlying cause. The Cause-of-Death Association Indicator is thus given by following formula:

$$CDAI_{u,c} = \frac{SP_{c/u}}{SP_c} = \frac{\sum_x \left( \frac{{}_u d_{c,x}}{{}_u d_x} . \overline{d}_x \right) \Big/ \sum_x \overline{d}_x}{\sum_x \left( \frac{d_{c,x}}{d_x} . \overline{d}_x \right) \Big/ \sum_x \overline{d}_x} * 100 = \frac{\sum_x \frac{{}_u d_{c,x}}{{}_u d_x} . \overline{d}_x}{\sum_x \frac{d_{c,x}}{d_x} . \overline{d}_x} * 100$$

${}_u d_{c,x}$ = number of deaths observed at age *x* with underlying cause *u* and contributing cause *c*;

${}_u d_x$ = number of deaths observed at age *x* with cause *u* as underlying cause;

$d_{c,,x}$ = number of deaths observed at age *x* with cause *c* as contributing cause (regardless of UCD);

$d_x$ = number of deaths observed at age *x* (regardless of UCD);

$\overline{d}_x$ = average number of deaths at age *x* in France and Italy.

**Summary results**

**Table 1: Standardized mortality rates (per 1,000,000) for each cause reported as Underlying cause or Multiple cause and Standardized Ratio of Multiple to Underlying cause (SRMU) – Neoplasms, France and Italy, 2003**

| | UNDERLYING CAUSE | | MULTIPLE CAUSE * | | SRMU | |
|---|---|---|---|---|---|---|
| | ITALY | FRANCE | ITALY | FRANCE | ITALY | FRANCE |
| Malignant neoplasm of lip, oral cavity, pharynx | 36 | 65 | 42 | 79 | 1,2 | 1,2 |
| Malignant neoplasm of oesophagus | 23 | 58 | 25 | 68 | 1,1 | 1,2 |
| Malignant neoplasm of stomach | 122 | 60 | 134 | 66 | 1,1 | 1,1 |
| Malignant neoplasm of small intestine, colon, rectum, anus and other/ill-defined digestive organs | 225 | 213 | 259 | 244 | 1,1 | 1,1 |
| Malignant neoplasm of liver, the intrahepatic bile ducts, gallbladder and other unspecified parts of biliary tract | 147 | 110 | 161 | 124 | 1,1 | 1,1 |
| Malignant neoplasm of pancreas | 96 | 91 | 101 | 95 | 1,1 | 1,0 |
| Malignant neoplasm of larynx and trachea/brochus/lung | 425 | 403 | 460 | 444 | 1,1 | 1,1 |
| Malignant melanoma of skin | 19 | 19 | 21 | 21 | 1,1 | 1,1 |
| Malignant neoplasm of skin | 5 | 6 | 7 | 8 | 1,5 | 1,5 |
| Malignant neoplasm of breast | 125 | 131 | 145 | 152 | 1,2 | 1,2 |
| Malignant neoplasm of cervix uteri and other parts of uterus | 27 | 33 | 32 | 38 | 1,2 | 1,2 |
| Malignant neoplasm of ovary | 33 | 37 | 36 | 40 | 1,1 | 1,1 |
| Malignant neoplasm of prostate | 94 | 122 | 129 | 166 | 1,4 | 1,4 |
| Malignant neoplasm of kidney | 35 | 40 | 41 | 47 | 1,2 | 1,2 |
| Malignant neoplasm of bladder | 58 | 56 | 75 | 70 | 1,3 | 1,2 |
| Malignant neoplasm of lymph./haematopoietic tissue | 153 | 150 | 191 | 185 | 1,2 | 1,2 |
| Malignant neoplasm of eye, brain and other parts of central nervous | 43 | 46 | 47 | 48 | 1,1 | 1,1 |
| Secondary malignant neoplasm | 14 | 0 | 733 | 651 | 53,6 | - |
| Malignant neoplasm of ill-defined/unspecified and independent (primary) multiple sites | 87 | 183 | 803 | 590 | 9,2 | 3,2 |
| Other malignant neoplasms | 65 | 64 | 76 | 75 | 1,2 | 1,2 |
| Benign neoplasms/Neoplasms of uncertain or unknown behaviour | 87 | 71 | 155 | 118 | 1,8 | 1,7 |
| **All NEOPLASMS** | **1918** | **1957** | **3348** | **3162** | **1,7** | **1,6** |
| **ALL DEATHS**** | **5620** | **5514** | **15069** | **11114** | **2,7** | **2,0** |

**Mechanisms of death and ill-defined contributing causes are excluded*

*** excluding deaths due to external causes and infant deaths*

*Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database*The impact of the

The impact of the MCOD approach, as far as the re-evaluation of the cancer-related mortality levels is concerned, is modest. The ranking of the mortality rates according to the anatomic site results almost unchanged. Table 1 shows that most site-specific values of the SRMU are very close to one. If we set apart the secondary malignant neoplasms that, "by definition", are mainly mentioned as contributing cause[2], the highest values are for the "malignant neoplasms of ill-defined/unspecified and independent primary multiple sites" (9.2 in Italy and 3.2 in France), for "benign neoplasms/neoplasms of uncertain or unknown behaviour" (1.8 in Italy and 1.7 in France), as well as for "malignant neoplasms of the skin and the subcutaneous tissue" (1.5 in both countries) and "malignant neoplasms of the prostate" (1.4 in both countries).

When looking at the standardized prevalence rates of the various combinations of causes[3], we find that for all anatomic sites, the most frequent associations are with neoplasms, diseases of the circulatory system, diseases of the respiratory system, as well as - but to a lesser extent - diseases of the digestive system or endocrine, nutritional and metabolic diseases. Since these groups of causes are the main killers in the two countries, we suspect that some of these associations are not specific to cancer-related mortality. And indeed, the examination of the CDAIs provides a quite different picture. Figure 1 (resp. figure 2) display the contributing (resp. the underlying) causes of death for which a neoplasm is more frequently than expected mentioned as underlying (resp. contributing) cause of the death. The next graphs (figure 3.1 for France and 3.2 for Italy[4]) display the CDAIs computed at a more detailed level of classification for all deaths with a malignant neoplasm as UDC[5].

On figures 1 and 2, the similarity of the results for the two countries is very striking. CDAIs for the frequent association between neoplasms and diseases of the circulatory/respiratory are lower than 100. In contrast, our analysis confirms that the simultaneous reporting of a neoplasm as underlying and contributing cause of the death is a feature of the cancer-related mortality. When a neoplasm is mentioned as contributing cause (figure 2), no other association has a CDAI over 100. Figures 3.1 and 3.2 show that for almost all anatomic sites as UDC, a secondary malignant neoplasm or a "malignant neoplasm of ill-defined/unspecified and independent primary multiple sites" are very frequently reported as contributing cause of the death. Other frequent associations involve proximate anatomic sites, like sites of the digestive system or the upper aerodigestive tract, reflecting the fact that cancers of any tissue are likely to spread to neighbouring tissue. Specifically to France, we find that "malignant neoplasms of larynx, trachea, brochus and lung" are frequently reported as contributing

[2] In France, there are very few deaths with a secondary malignant neoplasm as underlying cause, and the corresponding SRMU has not been computed.

[3] data not shown

[4] The cells of the table that result from the cross-matching of every site-specific malignant neoplasm as UDC and every contributing cause of death are colored according to the value of the corresponding CDAI. After computing the standard deviation ($\sigma$) of the CDAIs , we created five classes: $[0;100[$ , $[100;100+\sigma/4[$ , $[100+\sigma/4;100+\sigma/2[$ , $[100+\sigma/2;100+3\sigma/4[$ and $[100+3\sigma/4;\infty[$.The first class is white while all other classes are progressively darker shades of grey.

[5] Only malignant neoplasms with a well-defined anatomic sites are presented.

cause of a malignant neoplasm of oesophagus or a “malignant neoplasm of lip, oral cavity, pharynx”. Alcohol and tobacco use are likely to play a role in those deaths. Tobacco use is also likely to be involved in the strong association observed between “malignant neoplasm of bladder” and “malignant neoplasm of larynx, trachea, brochus and lung”, as well as between “malignant neoplasms of larynx, trachea, brochus and lung“ and “malignant neoplasm of prostate”. If the link between cigarette smoking and bladder cancer is well established (Sasco et al. 2004), there is some debate in the scientific community about a possible link between cigarette smoking and prostate cancer, perhaps through its effect on sex hormone metabolism (Matzkin et al. 1993; Van der Gulden et al. 1994).

When the underlying cause of the death is a neoplasm (figure 1), several associations with other groups of causes have high values of the CDAIs. As far as we know from the medical state of the art, they can be categorized according following lines of interpretation:

1 Cancer results from the **degeneration of the contributing cause.** Hence, the contributing cause preceded cancer. The strong association found in France and Italy (figures 3.1 and 3.2) between “malignant neoplasm of liver, the intrahepatic bile ducts, gallbladder and other unspecified parts of biliary tract” and both, viral hepatitis and chronic liver disease is emblematic of that situation.

2 The contributing cause is a **risk factor for cancer**. Specifically to France, alcohol and tobacco use[6] emerge as a frequent contributing cause of several neoplasms. In Italy, we find a frequent association between viral hepatitis (mainly: chronic viral hepatitis C) and “malignant neoplasm of lymphoid, haematopoietic and related tissue” (mainly: Non-Hodgkin's lymphoma) that, with conflicting results, has been documented in the medical literature (Mele et al. 2003).

3 The contributing cause and the cancer have a **common cause**. The role played by tobacco use in the association noted before between neoplasm of bladder and lung cancer illustrates this point. We suspect that the combination between “malignant neoplasm of larynx and trachea/bronchus/lung“ and tuberculosis that is found in both countries, and that is well documented too, reflects precarious social situations that are associated with higher risks for both conditions (e.g. tobacco use, exposure to silicosis). However, another explanation is possible. It is suggested that immunodeficiency due to the neoplastic disease itself or its therapy might cause a reactivation of a pre-existing “latent” tuberculosis (Kaplan et al. 1974).

4 The contributing cause is a **consequence or a complication of cancer**. Figure 1, 3.1 and 3.2 provide numerous examples of this situation. The strong association observed in both countries between “malnutrition and other nutritional deficiencies” and several anatomic sites of the upper aerodigestive tract/digestive system and is one of them. One possible consequence of those cancers is that the person cannot eat anymore. Similarly, we suspect that metastases to the bones are involved in the association between “other diseases of the musculoskeletal system/connective tissue” (mainly: pathological fractures) and several anatomic sites.

[6] **“**Mental and behavioural disorders due to use of tobacco” (ICD-10 F179 code) is classified in the “Other Mental and behavioural disorders” group.

Though it is probably difficult to distinguish between the two, it should be noted that the contributing cause may be a consequence of the neoplasm or of its therapy. The strong association between "diseases of the blood(-forming organs), immunological disorders" (mainly: anemia, thrombocytopenia, and immunodeficiency) and several anatomic sites potentially illustrates the latter case.

5 The contributing cause is a **symptom of cancer.** As an example, epilepsia is frequently reported on the death certificates with brain cancer as UCD.

This categorization is necessarily a bit oversimplified. In many cases, it is difficult to say whether an association belongs to one or another category. In the end, there remain a few strong associations which interpretation is problematic. The frequent associations between Alzheimer's disease and neoplasm of breast and bladder in France, and between arthrosis and neoplasm of breast in Italy are puzzling. It is also unclear why, specifically to France, "other diseases of the circulatory system" (mainly: pulmonary embolism**,** phlebitis and thrombophlebitis) emerge as a contributing cause for neoplasms of uterus, or why "other diseases of the nervous system" (mainly: benign intracranial hypertension, compression of brain**,** cerebral oedema) frequently contribute to deaths with a melanoma or a neoplasm of kidney as UCD.

**Selected References**


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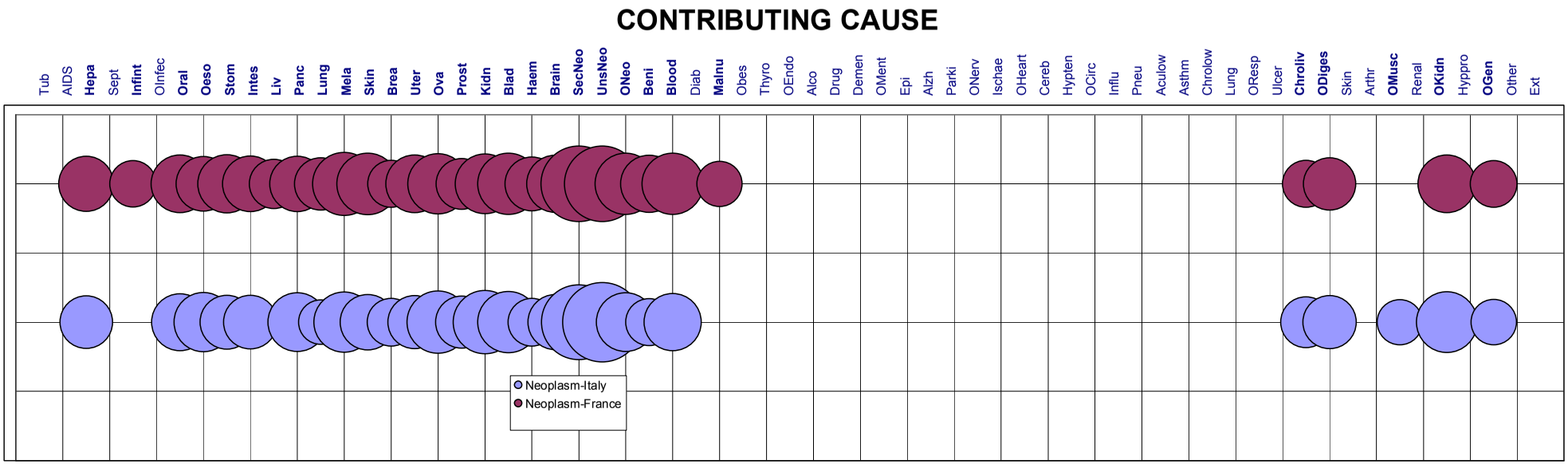
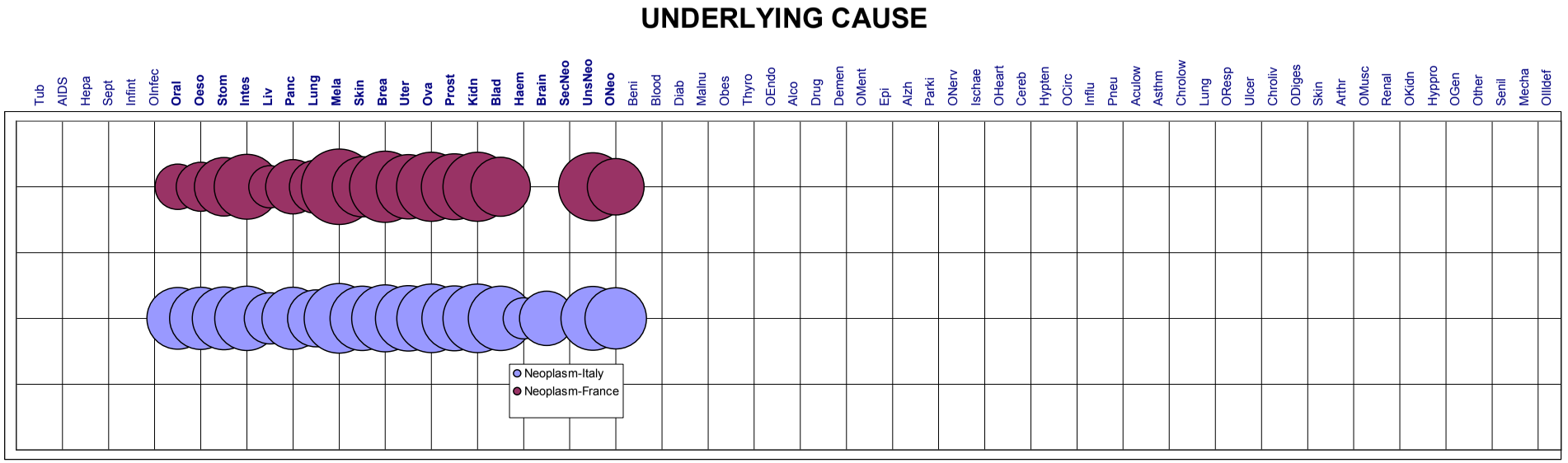
**Figure 1: CDAIs* - Neoplasms (all anatomic sites) as underlying cause of the death -France and Italy, 2003**



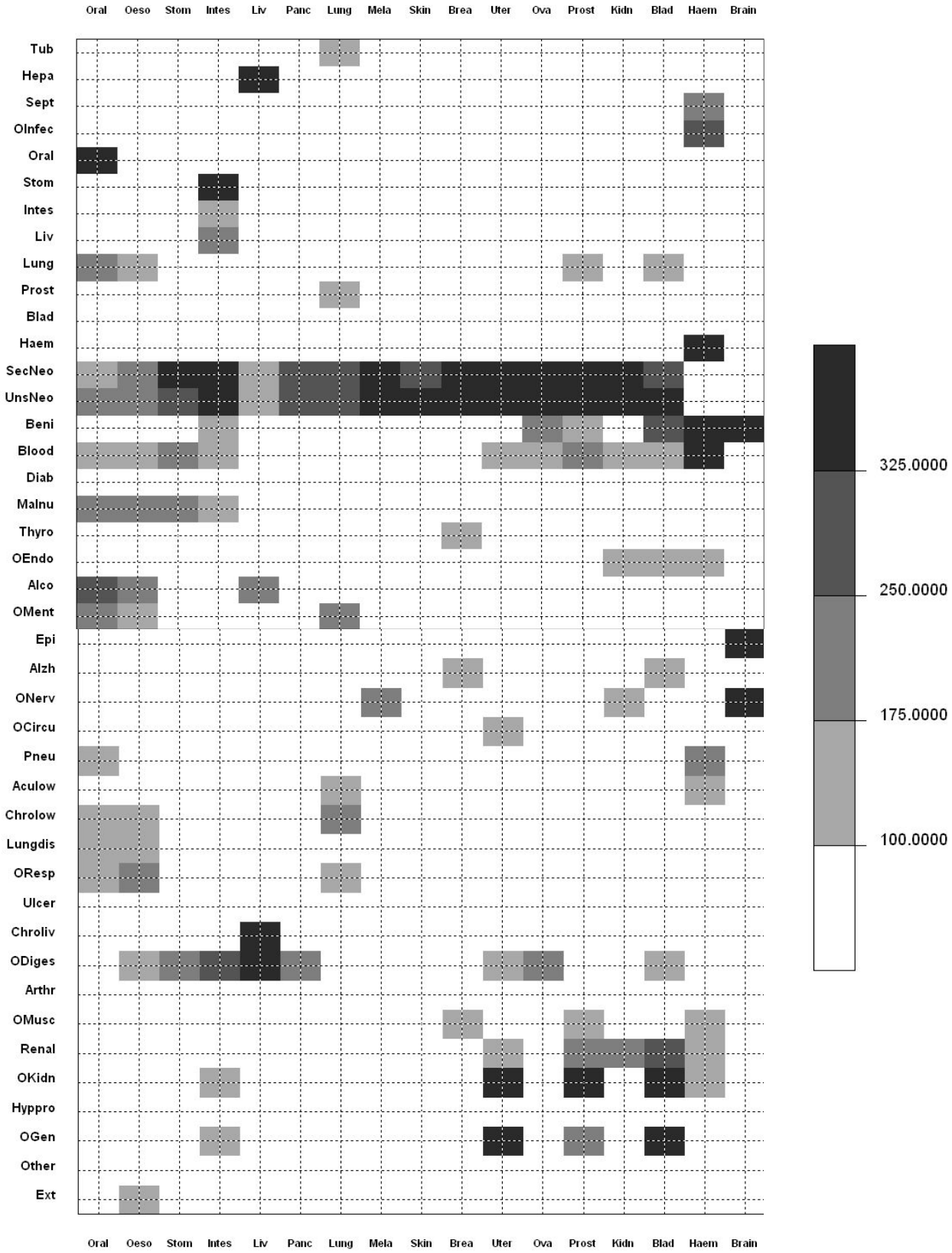

** Values of the indicator under 100 and/or corresponding to less than 50 cases are not shown*
*See abbreviations in the appendix*
*Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database*

**Figure 2: CDAIs* - Neoplasms (all anatomic sites) as contributing cause of the death - France and Italy, 2003**



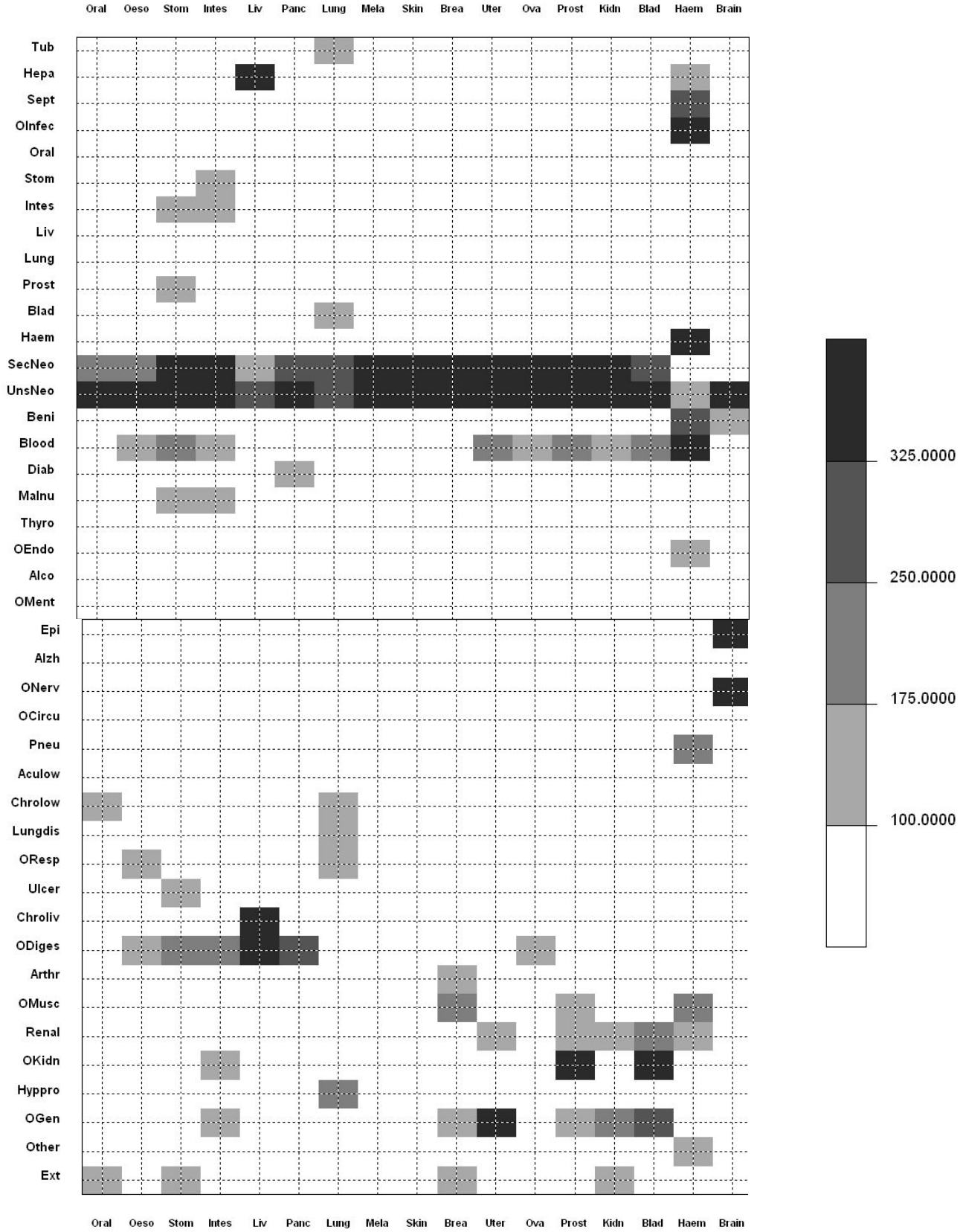

**Values of the indicator under 100 and/or corresponding to less than 50 cases are not shown*
*See abbreviations in the appendix*
*Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database*

**Figure 3.1: CDAIs* - Associations (Vertical axis) with neoplasms as underlying cause of the death (Horizontal axis) - France, 2003**




** Values of the indicator under 100 and/or corresponding to less than 50 cases are not shown*
*See abbreviations in the appendix*
*Data: Inserm CépiDc mortality database Italy: ISTAT mortality database*

**Figure 3.2: CDAIs - Associations (Vertical axis) with neoplasms as underlying cause of the death (Horizontal axis) - Italy, 2003**




** Values of the indicator under 100 and/or corresponding to less than 50 cases are not shown*
*See abbreviations in the appendix*
*Data: ISTAT mortality database*

# APPENDIX: Groups and Abbreviations

| Group # | Abb. | Groups and subgroups | ICD-10 code |
|---|---|---|---|
| **1** | **INF** | **Infectious and parasitic diseases** | |
| | Tub | Tuberculosis | A15-A19, B90 |
| | AIDS | AIDS (HIV-disease) | B20-B24 |
| | Hepa | Viral hepatitis | B15-B19, B94.2 |
| | Sept | Septicaemia | A40-A41 |
| | Intinf | Intestinal infectious diseases | A00-A09 |
| | OInfec | Other Infectious and parasitic diseases | (A00-B99) - Supra codes |
| **2** | **NEO** | **Neoplasms** | |
| | Oral | Malignant neoplasm of lip, oral cavity, pharynx | C00-C14 |
| | Oeso | Malignant neoplasm of oesophagus | C15 |
| | Stom | Malignant neoplasm of stomach | C16 |
| | Intes | Malignant neoplasm of small intestine, colon, rectum and anus, and other/ill-defined digestive organs | C17,C18-C21,C26 |
| | Liv | Malignant neoplasm of liver, the intrahepatic bile ducts, gallbladder and other unspecified parts of biliary tract | C22-C24 |
| | Panc | Malignant neoplasm of pancreas | C25 |
| | Lung | Malignant neoplasm of larynx and trachea/bronchus/lung | C32-C34 |
| | Mela | Malignant melanoma of skin | C43 |
| | Skin | Malignant neoplasm of skin | C44 |
| | Brea | Malignant neoplasm of breast | C50 |
| | Uter | Malignant neoplasm of cervix uteri and other parts of uterus | C53, C54, C55 |
| | Ova | Malignant neoplasm of ovary | C56 |
| | Prost | Malignant neoplasm of prostate | C61 |

| | | | |
|---|---|---|---|
| | Kidn | Malignant neoplasm of kidney | C64 |
| | Blad | Malignant neoplasm of bladder | C67 |
| | Haem | Malignant neoplasm of lymphoid, haematopoietic and related tissue | C81-C96 |
| | Brain | Malignant neoplasm of eye, brain and other parts of central nervous system | C69-C72 |
| | SecNeo | Secondary malignant neoplasm | C77-C79 |
| | UnsNeo | Malignant neoplasm of ill-defined/unspecified/ independent (primary) multiple sites | C76, C80, C97 |
| | ONeo | Other malignant neoplasms | (C00-C99) – Supra codes |
| | Beni | Benign neoplasms, in situ neoplasms and neoplasms of uncertain or unknown behaviour | D00-D09, D10-D36, D37-D48 |
| **3** | **BLOOD** | **Diseases of the blood(-forming organs), immunol.disorders** | D50-D89 |
| **4** | **ENDOC** | **Endocrine, nutritional and metabolic diseases** | |
| | Diab | Diabetes mellitus | E10-E14 |
| | Malnu | Malnutrition and other nutritional deficiencies | E40-E64 |
| | Obes | Obesity | E65-E68 |
| | Thyro | Disorders of thyroid gland | E00-E07 |
| | OEndo | Other Endocrine, nutritional and metabolic diseases | (E00-E90) - Supra codes |
| **5** | **MENT** | **Mental and behavioral disorders** | |
| | Alco | Alcoholic psychosis/chronic alcohol abuse | F10.1 to F10-9, G31.2 |
| | Drug | Drug dependence, toxicomania | F11-F16<br>Except F11.0, F12.0,F13.0, F14.0, F15.0, F16.0<br>F18-F19 except F18.0, F19.0 |
| | Demen | Dementias (excluding Alzheimer's) | F01, F03, G31.0, G31.8, G31.1, G31.9 |
| | OMent | Other Mental and behavioral disorders | (F00-F99) except F10.0, F11.0, F12.0, F13.0, F14.0, F15.0, F16.0, F17.0, F18.0, F19.0 - Supra ' F' codes |

| | | | |
|---|---|---|---|
| **6** | **NERV** | **Diseases of the nervous system** | |
| | Epi | Epilepsy | G40-G41 |
| | Alzh | Alzheimer's disease | G30 |
| | Parki | Parkinson's disease | G20, G21 |
| | ONerv | Other Diseases of the nervous system | (G00-G98) - (G31.0, G31.1 G31.2, G31.8, G31.9 ) and – Supra |
| **7** | **CIRC** | **Diseases of the circulatory system** | |
| | Ischae | Ischaemic heart diseases | I20-I25 |
| | OHeart | Other heart diseases | I30-I33, I39-I45, I47-I48, I49.1-I52, I00-I09 |
| | Cereb | Cerebrovascular diseases | I60-I69 |
| | Hypten | Hypertensive diseases | I10-I15 |
| | OCirc | Other Diseases of the circulatory system | (I00-I99) – (I46, I49.0, I95.9, I99) – Supra codes |
| **8** | **RESP** | **Diseases of the respiratory system** | |
| | Influ | Influenza | J10-J11 |
| | Pneu | Pneumonia | J12-J18 |
| | Aculow | Other acute lower respiratory diseases | J00-J09, J19-J22 |
| | Asthm | Asthma | J45-J46 |
| | Chrolow | Other chronic lower respiratory diseases | J40-J44 |
| | Lungdis | Lung diseases due to external agents | J60-J70 |
| | OResp | Other diseases of the respiratory system | (J00-J99) (J96.0, J96.9) – Supra codes |
| **9** | **DIGES** | **Diseases of the digestive system** | |
| | Ulcer | Ulcer of stomach, duodenum and jejunum | K25-K28 |
| | Chroliv | Chronic liver disease | K70, K73-K74 |
| | ODiges | Other Diseases of the digestive system | (K00-K93) – Supra codes |

| | | | |
|---|---|---|---|
| **10** | **SKIN** | **Diseases of the skin and subcutaneous tissue** | **L00-L99** |
| **11** | **MUS** | **Diseases of the musculoskeletal system/connective tissue** | |
| | Arthr | Rheumatoid arthritis and osteoarthrosis | M05-M06, M15-M19 |
| | OMusc | Other diseases of the musculoskeletal system/connective tissue | (M00-M99) – Supra codes |
| **12** | **GEN** | **Diseases of the genitourinary system** | |
| | Renal | Renal failure | N17-N19 |
| | OKidn | Other Diseases of kidney and ureter | N00-N16 |
| | Hyppro | Hyperplasia of prostate | N40 |
| | OGen | Other diseases of the genitourinary system | (N00-N99) – Supra codes |
| **13** | **OTHER** | **Other diseases** | |
| | Pregn<br><br>Perinat<br>Malfor<br><br>Eye<br>Ear<br>SIDS | Complications of pregnancy, childbirth and puerperium<br>Certain conditions originating in the perinatal period<br>Congenital malformations and chromosomal abnormalities<br>Diseases of the eye and adnexia<br>Diseases of the ear and mastoid process<br>SIDS | O00-O99<br>(P00-P96)- P28.5<br>Q00-Q99<br>H00- H59<br>H60- H95<br>R95 |
| **14** | **ILLDEF** | **Symptoms, signs, abnormal findings and ill-defined causes** | |
| | Senil | Senility | R54 |
| | Mecha | Mechanisms of the death ° | I46, I49.0, R09.2, R40.2, R57 |
| | OIlldef | Other Symptoms, signs, abnormal findings and ill-defined causes °° | (R00-R94), (R96-R99), I95.9, I99, J96.0, J96.9, P.28.5, U00 - Supra R codes |
| **15** | **EXT** | **External causes** | S, T, V, W, X Y codes<br>F10.0, F11.0, F12.0,F13.0, F14.0,F15.0, F16.0,F17.0, F18.0,F19.0 |

°) Cardiac arrest (I46.0), Ventricular fibrillation (I49.0), Respiratory arrest (R09.2), Coma (R40.2), Shock (R57)
°°) Hypotension (I95.9), Other unspecified disorders of circulatory system (I99), Acute respiratory failure (J96.0), Respiratory failure unspecified (J96.9), Respiratory failure of newborn P(.28.5)