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Tukenova, Markhaba; Diallo, Ibrahima; Anderson, Harald; Hawkins, Mike; Garwicz, Stanislaw; Sankila, Risto; El Fayech, Chiraz; Winter, Dave; Rubino, Carole; Adjadj, Elisabeth; Haddy, Nadia; Oberlin, Odile; Möller, Torgil; Langmark, Froydis; Tryggvadottir, Laufey; Pacquement, Helene; Svahn-Tapper, Gudrun; de Vathaire, Florent

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Second malignant neoplasms in digestive organs after childhood cancer: a cohort-nested case-control study.

Markhaba Tukenova\textsuperscript{1,2,3} Ph.D., Ibrahima Diallo\textsuperscript{1,2,3} Ph.D., Harald Anderson\textsuperscript{4} Ph.D., Mike Hawkins\textsuperscript{5} Ph.D., Stanislaw Garwicz \textsuperscript{6} Ph.D., Risto Sankila\textsuperscript{7} Ph.D., Chiraz El Fayech\textsuperscript{1,2,3} M.D., Dave Winter\textsuperscript{5} Ph.D., Carole Rubino\textsuperscript{1,2,3} Ph.D., Elisabeth Adjadj\textsuperscript{1,2,3,8} Ph.D., Nadia Haddy\textsuperscript{1,2,3} Ph.D., Odile Oberlin\textsuperscript{1,2,3} M.D., Torgil Moller\textsuperscript{4} Ph.D., Froydis Langmark\textsuperscript{7} M.D., Laufey Tryggvadottir\textsuperscript{9} Ph.D., Hélène Pacquement\textsuperscript{8} M.D., Gudrun Svahn-Tapper\textsuperscript{4} Ph.D., Florent de Vathaire\textsuperscript{1,2,3} Ph.D.

1 Radiation Epidemiology Group, CESP Center for Research in Epidemiology and Population Health, U1018, Inserm, F-94807, Villejuif, France
2 University Paris Sud 11, UMRS 1018, F-94807, Villejuif, France
3 Gustave Roussy Institute, F-94805, Villejuif, France
4 Department of Cancer Epidemiology, Lund University, Sweden
5 Center for Childhood Cancer Survivor Studies, Department of Public Health & Epidemiology, University of Birmingham, UK
6 Childhood Cancer Research Center, University Children’s Hospital, SE-22185 Lund, Sweden
7 Finnish Cancer Registry, Helsinki, Finland
8 Curie Institute, Paris F-75005 Paris, France
9 Norwegian Cancer Registry, Oslo, Norway

Corresponding author
Florent de Vathaire
INSERM U605
ABSTRACT

Purpose: Cancers of the digestive system constitute a major risk for childhood cancer survivors treated with radiotherapy once they reach adulthood. The aim of this study was to determine therapy-related risk factors for the development of a second malignancy in the digestive organs (SMDO) after a childhood cancer.

Methods: Among 4,568 2-year survivors of a childhood solid cancer diagnosed prior to 17 years of age at eight French and British centers, and 25,120 patients diagnosed as having a malignant neoplasm before the age of 20, extracted from the Nordic Cancer Registries, we matched 58 cases (17 women and 41 men) of SMDO and 167 controls, in their respective cohort, for sex, age at first cancer, calendar year of occurrence of the first cancer and duration of follow-up. The radiation dose received at the site of each second malignancy and at the corresponding site of its matched control was estimated.

Results: The risk of developing a SMDO was 9.7-fold higher in relation to the general populations in France and the United Kingdom. In the case-control study, a strong dose-response relationship was estimated, compared to survivors who had not received radiotherapy, the odds ratio was 5.2 (95%CI: 1.7-16.0) for local radiation doses between 10 and 29 Gy and 9.6 (95%CI: 2.6-35.2) for doses equal to or greater than 30 Gy. Chemotherapy was also found to increase the risk of developing SMDO.

Conclusions: This study confirms that childhood cancer treatments strongly increase the risk of SMDO, which occur only after a very long latency period.

Short title: Second malignant neoplasms in digestive organs after childhood cancer.

Key words: childhood cancer, second malignancy in the gastrointestinal tract, radiotherapy, chemotherapy.
Abbreviations: SMN: second malignant neoplasm(s); FMN: first malignant neoplasm(s); SMDO: second malignancy in digestive organs; SMDT: second malignancy in digestive tract; SIR: standardized incidence ratio; AER: annual excess risk; CI: confidence interval, OR: odds ratio; CCSS: Childhood Cancer Survivors Study.

Conflict of interest:

We declare no conflicts of interest.
It is generally recognized that long-term survivors of childhood cancer are at a substantially increased risk of developing second malignant neoplasms (SMN) at a broad spectrum of anatomic sites following exposure to chemotherapy and radiotherapy. The importance of genetic factors must also be considered. Unlike leukemia, solid tumors generally occur much later following treatment of the first malignancy. Pediatric survivors experience significantly increased risk of cancers of the female breast, thyroid, digestive tract, lung, bone and connective tissue. However, digestive system cancers account for about half of the cancers in excess diagnosed in atomic bomb survivors, and thus might also be the case in survivors of childhood cancer. The etiology and risk factors are incompletely understood, but often include chemotherapy agents and ionizing radiation, while the risk increases with increasing follow-up after radiation and if exposure occurred at a young age.

Risk of colorectal cancers was shown not to increase until 10 years after the diagnosis of childhood Hodgkin's disease and remained elevated for at least a decade, suggesting late radiogenic effects, although data are currently insufficient to ascertain whether the increased risk persists. Radiation exposure has been reported to increase a second malignancy in digestive organs (SMDO) in irradiated adult groups. Likewise, results from analysis of the large-scale Childhood Cancer Survivor Study (CCSS) found that gastrointestinal carcinomas were associated with radiation and alkylating agent therapy. However, very limited data are available on dose-related risks in childhood cancer survivors. The main objective of this population-based case-control study was to estimate the relationship between radiotherapy doses received at a given site in the digestive tract and risk of SMDO at that site, in order to determine the risk conferred by radiation therapy.
METHODS

Study population

French and UK cohort

An initial cohort which included 4,590 2-year survivors of childhood cancer treated in, or before the end of, 1985 at eight cancer centers in France and the UK for all types of FMN (with the exception of leukemia) was created between 1985 and 1995. A total of 4,568 patients treated before the age of 17 were included. UK patient follow-up was traced using the National Health Service Central Registers. Follow-up for French patients were assessed using the medical records from the treatment centers, and was also updated from September 1st, 2005 using a self-questionnaire. This very wide-scale questionnaire provided information on socioeconomic status, cancer risk factors, quality of life and health outcome and was based on that of the BCSS. A total of 2,546 patients who were still alive were considered eligible. A questionnaire was sent by regular mail to the 2,095 patients for whom we had obtained the most recent address from the National Health Insurance System and who had sent back a signed consent agreement. This agreement included an authorization to contact the medical practitioner and medical facilities. A total of 1,791 (70%) patients returned the completed questionnaire by December 31, 2008.

Cohort study

The cohort study focused exclusively on the French-UK cohort. Results concerning the Nordic cohort had been reported in a previous publication. There were 3,350 French individuals who were followed up until the date of the occurrence of a SMDO, the date of death, the date of response to the self-questionnaire or the date of the
last medical contact, whichever occurred first. There were 1218 British individuals who were followed up through December 2005 until the date of the occurrence of a SMDO or until the date of death, whichever occurred first.

The expected number of SMDO was obtained for each gender, 5-year age group and 5-year calendar period, by multiplying the reference incidence rates by the number of person-years at risk. We used estimates of the French national cancer incidence rates for patients treated at French centers and the United Kingdom national cancer incidence rates for those treated in the UK as reference rates. The standardized incidence ratio (SIR), calculated as the ratio between the observed number of SMDO and the expected number, was considered to follow a Poisson distribution. The annual excess risk (AER) was calculated as the difference between the observed and expected number of SMDO, divided by the number of person-years of follow-up. AMFIT Software was used for cohort analysis.

**Nordic cohort**

The Nordic cohort was simply used to provide additional cases and controls for the nested case-control portion of the study. This cohort included 25,120 childhood cancer patients diagnosed as having a malignant neoplasm before the age of 20 years recorded in one of the five Nordic National Cancer Registries (Denmark, Finland, Iceland, Norway, and Sweden) between 1960 and 1987 and followed up through December, 31st 1991 for the date of occurrence of SMN, date of death or date of emigration, whichever occurred first, by cross-linking with national cancer registries. All 5 cancer registries are population-based, with very good coverage of incident cancers. Data collection and coding methods employed by each registry have previously been described in detail. In contrast with the French-UK cohorts,
chemotherapy and dosimetry estimates were carried out only for cases and controls\textsuperscript{19}.

**Case ascertainment**

SMDO eligible for inclusion in this analysis fell into the International Classification of Diseases of Oncology (ICDO-0) as 150 to 159 (excluding 158). Tumors of the digestive tract (SMDT: excluding liver, pancreas and digestive tract unspecified) (ICDO-0) 150 to 154 were analyzed separately. Sixteen validated SMDO cases\textsuperscript{20} from the Nordic cohort were included. We identified, via a self-questionnaire and medical records, 56 SMDO cases in the French-UK cohort, among whom 42 were included and 14 were excluded for the following reasons: no historical information on deceased patients (n=7), relapse of the initial tumor or metastasis (n=4) and peritoneal tumor (n=3). Finally, 58 cases were included in the present study.

**Case-control study**

Each case was matched with 3 controls (52 cases), 2 controls (5 cases) and 1 control (1 case) selected from among all patients from the respective cohort according to sex, age at first cancer (±3 years) and calendar year of occurrence of FMN (±3 years, except for 1 control, diagnosed at +6 years), totaling 167 controls (118 males and 49 females). Controls had to be followed up over a period that was at least equal to the interval between the first and second cancer of the matched case. This period was defined as the follow-up period. Conditional logistic regression was used to analyze the risk of a SMDO as a function of radiation, chemotherapy and interaction between various exposures\textsuperscript{21}. Multivariate analysis was adjusted for the type of first cancer diagnosis. For variables related to radiotherapy, adjusted OR and p-values were
estimated, controlling for chemotherapy (yes/no); for variables related to chemotherapy, the same parameters were estimated, controlling for local dose of radiation (categorized variable). To allow for possible synergistic effects of local radiotherapy and chemotherapy, we tested interactions. All confidence intervals (CI) and tests were 2-sided.

**Radiation dosimetry**

Radiotherapy data were obtained from technical radiotherapy records by hospital physicists. Individual doses were calculated with the homemade Dos_EG software package\textsuperscript{22-23}. The local radiation dose was defined as the cumulative absorbed dose at the site of the SMDO for each case, and a similar site for its matched controls. Since dosimetric reconstruction was not possible for 3 controls, we considered their data as missing in multivariate analysis. To assess the effect of the radiation dose, the local dose was analyzed as a categorized variable (no radiotherapy, <9 Gy, 10-29 Gy, 30 Gy or more).

**Chemotherapy measurement**

Drugs were classified according to the following categories: epipodophyllotoxins, anthracyclines, alkylating agents, vinca alkaloids, antimetabolites and antibiotics. A detailed description of chemotherapy administered to this cohort has been previously published\textsuperscript{24}.
RESULTS

Cohort study

After 102,858 person-years and a median follow-up of 25 years (range, 2 to 63) the risk of a SMDO after initial childhood cancer was 9.7 times greater than that in the general population (95% CI: 7.0 to 12.8), with significantly increased risk of cancers of the stomach, liver, pancreas, colon and rectum (Table 1). The risk of SMDO varied with therapy. Chemotherapy alone and combined modality therapy were associated with a significantly increased risk of developing SMDO (SIR=9.1, 95% CI: 2.3 to 23.6; SIR=29.0, 95% CI: 20.5 to 39.8, respectively). Patients treated with radiotherapy alone had a SIR of 1.0 (CI, 0.2 to 3.0), which was not statistically significant.

The overall AER was 31.5 cases per 100,000 person-years of follow-up (95% CI: 21.0 to 44.7). When the time since diagnosis of the first cancer was taken into account, the SIR decreased (p-trend<.001). In contrast, the AER increased considerably (p-trend <.001) over time following the first cancer, from 2.5 additional cases annually per 100,000 persons between 2 to 10 years after diagnosis, to 116.2 additional cases 40 years or more thereafter (Figure 1).

Risk attributable to high radiation doses

In the cohort study, 889 patients (19.5%) had received an average radiation dose to the digestive organs of over 10 Gy, and 22 developed a SMDO. At 35 years or more after treatment, for patients who had received an average dose of less than 10 Gy to the digestive organs, there was a risk of having 126 new cases in excess each year.
for 100,000 person-years of follow-up (95% CI; 41 to 263); among those who had received more than 10 Gy, the AER was multiplied by 5.8 (AER = 731, 95% CI 293 to 1,450).

**Live style risk factors**

Of the 1791 patients who sent back the questionnaire, 29% declared themselves as current regular smokers at time of questionnaire, this proportion being 33% in men and 26% in women. The average daily declared consumption of alcohol was 0.80 gram in men and 0.34 in women.

Because only 14 of the 41 cases of SMDO were observed in patients who fulfilled the questionnaire, we were not able to investigate the role of life style factors in the risk of SMDO.

**Case-control study**

In 58 cases, nephroblastoma (27.6%), Hodgkin’s disease (25.9%) and soft tissue sarcoma (13.8%) were the most frequent FMN, whereas tumors of the colon (41.4%), esophagus and stomach (24.1%) were predominantly SMN. The median age at FMN was 5.4 years, and it was 33.2 years at diagnosis of the SMN (Table 2). The median interval between the first and second diagnoses was 23.5 years, with the shortest interval being for SMN in the pancreas (median 20.5 years) and the longest for SMN in the colon (median 27 years). Forty-seven cases (81%) and 115 controls (69%) received radiotherapy. The mean local dose was 18.1 Gy for cases (range 0-71) and 7.5 Gy for controls (range 0-57.5). In multivariate analysis, we included the local dose of radiation and drugs such as alkylating agents, vinca alkaloids and anthracyclines, which had been associated with a significantly increased OR in univariate analysis (Figure 2). When adjusted for chemotherapy, risk of a SMDO or SMDT was not significantly higher after radiotherapy (OR = 1.8 and 1.6; 95% CI: 0.8 to...
4.1 and 0.6 to 4.2, respectively), compared to those who had not received radiotherapy. When the local dose of radiation was taken into account, the risk increased sharply with increasing doses of radiation to the site of SMDO development (p-trend<.001) (Figure 3), and specifically for local doses attaining 10-29 Gy (OR=5.2; 95% CI: 1.7 to 16.0) and 30 Gy or more (OR=9.6; 95% CI: 2.6 to 35.2) (Figure 3). This risk was higher when SMDT was taken into account (OR=8.1 and 12.2; 95% CI: 1.6 to 40.2 and 2.1 to 71.5, respectively).

Thirty-nine cases (67%) and 80 controls (45%) had received chemotherapy. After adjusting for radiotherapy, exposure to chemotherapy increased the risk of a SMDO (OR=2.5; 95%CI: 1.04 to 5.8). No significant association was found between any of the drugs and risk of SMDO or SMDT when taking into account the radiation dose (Figure 3).

No significant interaction was found between drug categories (coded yes/no) and the local radiation dose.

Overall, in a linear relative risk model, each gray to the digestive organs increased the OR of SMDO of 13% (95%CI: 5% to 32%), this value being non significantly (Chi-2=0.4, p=0.5) different between men (OR=15%, 95%CI: 5% to 35%) and women (OR=8%, 95%CI: -1% to 44%).

DISCUSSION

Our French-UK cohort was at a 9.7-fold increased risk of developing a SMDO compared to the general French-British population. Despite a decrease in the SIR with time since follow-up, a strong increase in AER was observed during the last 40 years of follow-up. In a nested case-control study, we identified a dose-response
relationship where in the risk of developing a SMDO or SMDT increased with increasing local radiation doses. This risk was particularly high in patients who had received a radiation dose of 10 Gy or more to the digestive organs. Although chemotherapy was found to increase the risk of developing a SMDO or SMDT, we were unable to find a specific drug or drug category responsible for this increase.

The strong point of this study was that the histology of all cases was validated and the SMDO site considered in each case for the calculation of the local dose was similar to that of matched controls. A major limitation to our study was that we were unable to take into account potential confounding factors such as tobacco and alcohol consumption. Indeed, the risk of various cancers, including those of the upper aerodigestive tract, liver, stomach and colon/rectum, increases with tobacco and alcohol consumption, alone or in combination with dietary habits. However, data on tobacco and alcohol consumption was only available for French patients who completed the self-questionnaire (12 SMDO cases), mostly due to higher mortality for SMDO, 23 SMDO cases had died and thus had not filled in the questionnaire.

Additionally, it has to be noted that childhood cancer survivors in UK and in our cohort (data not shown) have a lower tobacco and alcohol consumption than the general population of their respective country.

Genetic factors have an established role in digestive cancers, in particular colorectal cancer. Even when adjusting for radiation dose to studied organs, genetic factors play also a role in second cancer risk following childhood cancer (Kony) and in particular in colorectal as a second malignancy (Rubino). Nevertheless we were not able to investigate these factors because this information was available for only 14 of the 58 SMDO.
Results of the cohort study must be compared to findings from the 3 major childhood survivor studies which provided information on long-term risk of SMDO: the Nordic population-based cohort of 47,697 5-year survivors followed for around 10 years found 123 SMDO \(^{31}\); the British population-based cohort (BCCSS), which followed up 16,541 3-year survivors for 10 years, found 32 SMDO \(^{8}\); and a CCSS study of 13,136 5-year survivors followed up for 15 years found 16 SMDO \(^{16}\).

The long period of follow-up (25 years on an average) and the decreasing SIR suggest that the SIR of SMDO should have been lower in our cohort than in those of previous studies. However, the observed SIR=9.7 in our report was similar to that in the UK population-based cohort (BCCSS) (SIR=9.1) \(^{8}\) and higher than those of the Nordic childhood (SIR=3.2) \(^{31}\) and CCSS cohorts (SIR=5.0, excluding the colon and rectum) \(^{16}\). These differences might be explained by different follow-up and therapeutic practices since, in hospital-based series like ours, which generally include patients with more extended tumors and more aggressive treatment, there exists a substantially greater risk of SMN than in population-based series \(^{8,31}\).

Up until now, little detailed information has existed on time variations in SIR and AER for digestive cancers. A variation in the temporal pattern similar to ours (the SIR decreased and the AER increased with follow-up) has been observed in adult followed an average of 11 years after Hodgkin’s disease \(^{12}\). However, the study of 5,925 subjects treated before the age of 21 years for Hodgkin's disease and followed 10.5 years on average, reported increasing SIR and AER which decreased after the age of 40, for all digestive SMN \(^{32}\). These observations suggest that risk of SMDO in young adults is increasing and persists throughout the duration of follow up.

In our cohort study, increased risk was found for patients exposed to both radiotherapy and chemotherapy as well as for those treated only with chemotherapy.
Combined radiotherapy has been reported to significantly increase the risk of gastrointestinal cancer in studies on HD adolescents, young adults\textsuperscript{33} and adults\textsuperscript{12-13}. The CCSS study found that risk of gastrointestinal carcinomas (excluding the colon and rectum) after treatment for all cancers was significantly associated with chemotherapy (SIR=7.4) and radiotherapy (SIR=7.0)\textsuperscript{16}. In contrast, several HD series did not observe any effect of radiotherapy\textsuperscript{12-13, 33} or chemotherapy\textsuperscript{12-13, 34}. However, treatment risk is difficult to compare and evaluate, since most reports did not provide detailed information concerning therapeutic exposure.

In our case-control study, we observed significantly increased risk of SMDO with local radiation dose. Interestingly, a similar finding was reported among atomic bomb survivors in Japan, whereas a statistically significant excess risk of cancer of the digestive system was 0.38 for 1 Sivert (95\%CI: 0.25 to 0.52)\textsuperscript{15}. However, a Nordic study which included 22 cases and 60 controls (16 cases and 42 controls were included in the present study) revealed a significantly increased risk of developing tumors of the digestive tract, including the oral cavity and pharynx, but only for doses of 30 Gy or more (RR=17.6; 95\% CI: 2.1 to 148.4) compared to the risk in non-irradiated patients)\textsuperscript{19}. In the French-UK cohort, survivors who had received over 10 Gy to the digestive organs during radiotherapy had 731 additional SMDO cases in excess annually per 100 000 person-years of observation 35 years or more after childhood treatment.

Although 71\% of the SMDO cases were men, and only 29\% women, we were not able to explain this difference. Nevertheless, it has to be noted that, although non significantly, the OR per gray in men was almost 2 times the one in women. Men could be more radiosensitive than women, for various reason including a higher
proportion of cofactors such as tobacco and alcohol, that we are unable to investigate in detail.

Although we observed an increased risk of developing SMDO after chemotherapy, the Nordic study did not show this risk increase, probably because of the small number of cases. Due to the frequency and heterogeneity of drug associations in our cohort, we were not able to adequately investigate the role of each drug or type of drug.

In conclusion, longer follow-up in this French-UK cohort showed that cancers of the digestive organs, usually observed in middle-aged adults and the elderly in a general population, occur at a much younger age after childhood cancer treatment and are likely to pose a serious problem for a growing number of long-term cancer survivors. Elucidating the role of treatments in this increase will require more detailed international pooled analyses.
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REFERENCES


**Figure legends**

Figure 1.

* Medical follow-up

Figure 2.

* Observed/Expected

Figure 3

* Multivariate model adjusting to type of first cancer diagnosis. For variables related to radiotherapy, the adjusted OR and p-value estimated controlling for chemotherapy (yes/no). For variables related to chemotherapy, the adjusted and p-value were estimated controlling for local radiation dose (categorized variable).
Table 1. SMDO cancer risk in 4,568 2-year survivors of a childhood cancer in France-UK cohort according to therapy.

<table>
<thead>
<tr>
<th>Second malignant neoplasms (Sites)</th>
<th>Observed</th>
<th>Expected</th>
<th>Standardized incidence ratio</th>
<th>Annual excess risk /100,000 persons</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>42</td>
<td>4.40</td>
<td>9.7 (7.0-12.8)</td>
<td>31.5 (21.0-44.7)</td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>1</td>
<td>0.51</td>
<td>2.0 (0.1-8.6)</td>
<td>0.9 (0.1-4.2)</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>8</td>
<td>0.61</td>
<td>13.2 (6.0-24.5)</td>
<td>6.7 (2.7-13.4)</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>4</td>
<td>0.40</td>
<td>9.9 (3.1-23.1)</td>
<td>3.3 (0.7-8.4)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>10</td>
<td>0.40</td>
<td>25.3 (12.7-44.3)</td>
<td>8.7 (3.9-16.0)</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>19</td>
<td>2.62</td>
<td>7.2 (4.4-10.9)</td>
<td>12.3 (5.9-21.3)</td>
<td></td>
</tr>
<tr>
<td>Therapy for all cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>0.78</td>
<td>2.6 (0.4-7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (alone)</td>
<td>3</td>
<td>0.33</td>
<td>9.1 (2.3-23.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (alone)</td>
<td>2</td>
<td>2.07</td>
<td>1.0 (0.2-3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined modality therapy</td>
<td>35</td>
<td>1.21</td>
<td>29.0 (20.5-39.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% Confidence Interval.
Table 2. Characteristics of cases according to SMDO site.

<table>
<thead>
<tr>
<th>Characteristics of cases</th>
<th>All SMN</th>
<th>Liver</th>
<th>Esophagus</th>
<th>Stomach</th>
<th>Colon</th>
<th>Pancreas</th>
<th>Digestive tract unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France / UK</td>
<td>42</td>
<td>10 (23.8)</td>
<td>1 (2.4)</td>
<td>7 (16.6)</td>
<td>19 (45.3)</td>
<td>4 (9.5)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Nordic countries</td>
<td>16</td>
<td>3 (18.75)</td>
<td>3 (18.75)</td>
<td>8 (50.0)</td>
<td>2 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex¹ n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (71)</td>
<td>10 (100)</td>
<td>4 (100)</td>
<td>8 (80)</td>
<td>14 (52)</td>
<td>5 (83)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (29)</td>
<td>0</td>
<td>0</td>
<td>2 (20)</td>
<td>13 (48)</td>
<td>1 (17)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Age at diagnosis of the first cancer¹ (median, range)</td>
<td>6.5 (0-19)</td>
<td>4.5 (0-14)</td>
<td>14.0 (0-19)</td>
<td>11.5 (1-19)</td>
<td>9.0 (0-19)</td>
<td>7.5 (1-16)</td>
<td>3.0</td>
</tr>
<tr>
<td>Age at diagnosis of the second cancer (median, range)</td>
<td>32.0 (11-59)</td>
<td>31.0 (18-50)</td>
<td>37.0 (28-47)</td>
<td>28.0 (18-48)</td>
<td>37.0 (15-59)</td>
<td>29.5 (11-48)</td>
<td>40.1</td>
</tr>
<tr>
<td>Latency period between 1st and 2nd cancer¹ (median years, range)</td>
<td>23.5 (2-49)</td>
<td>22.5 (13-49)</td>
<td>25.0 (23-28)</td>
<td>17.0 (2-45)</td>
<td>27.0 (5-46)</td>
<td>20.5 (9-38)</td>
<td>36.0</td>
</tr>
<tr>
<td>Local dose of radiation received at the site of second cancer² (mean Gy)</td>
<td>16.3 (0-71.0)</td>
<td>17.4 (0.1-71.0)</td>
<td>42.0 (30.8-48.2)</td>
<td>21.2 (0-45.6)</td>
<td>4.7 (0-42.6)</td>
<td>28.5 (0.3-38.2)</td>
<td>44.3</td>
</tr>
</tbody>
</table>
1Matching variable
2For patients who received radiotherapy
Figure 1. Temporal trend of SMDO in France-UK cohort according to follow-up

<table>
<thead>
<tr>
<th>Follow-up period from diagnosis (in years)*</th>
<th>Observed / Expected</th>
<th>Standardized incidence ratio (95%CI) p-trend</th>
<th>The annual excess risk (95%CI) p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10</td>
<td>1/0.09</td>
<td>10.7</td>
<td>2.5</td>
</tr>
<tr>
<td>10-20</td>
<td>14/0.33</td>
<td>42.6</td>
<td>36.7</td>
</tr>
<tr>
<td>20-30</td>
<td>11/1.00</td>
<td>11.4</td>
<td>35.2</td>
</tr>
<tr>
<td>30-40</td>
<td>9/1.48</td>
<td>6.1</td>
<td>65.2</td>
</tr>
<tr>
<td>40 or more</td>
<td>7/1.67</td>
<td>4.2</td>
<td>116.2</td>
</tr>
</tbody>
</table>

* Medical follow-up
Figure 2. Odds Ratio of SMN in digestive organs and digestive tract with exposure to different treatment modalities. Univariate analysis.

<table>
<thead>
<tr>
<th>Treatment modalities</th>
<th>O/E*</th>
<th>SMN in digestive organs</th>
<th>p-trend</th>
<th>SNN in digestive tract (esophagus, stomach and colon)</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local dose of radiation (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposition</td>
<td>9/37</td>
<td>10</td>
<td>&lt;0.001</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-9</td>
<td>16/85</td>
<td>1.1</td>
<td></td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>10-29</td>
<td>16/18</td>
<td>6.2</td>
<td></td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>30 or more</td>
<td>15/9</td>
<td>12.8</td>
<td></td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>16/37</td>
<td>2.2</td>
<td></td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Vinca alkaloides</td>
<td>24/50</td>
<td>3.2</td>
<td></td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Epipodophyllotoxins</td>
<td>4/3</td>
<td>3.5</td>
<td></td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>15/22</td>
<td>3.9</td>
<td></td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>7/14</td>
<td>1.7</td>
<td></td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>21/44</td>
<td>2.1</td>
<td></td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

* Observed/Expected
Figure 3. Odds Ratio of SMN in digestive organs and digestive tract with exposure to different treatment modalities. Multivariate analysis.

*Multivariate model adjusting to type of first cancer diagnosis. For variables related to radiotherapy, the adjusted OR and p-value estimated controlling for chemotherapy (yes/no).

For variables related to chemotherapy, the adjusted and p-value were estimated controlling for local radiation dose (categorized variable).