



HAL
open science

CORALE project: Cumulative lifetime multi-exposures to ionizing radiation and other risk factors and associations with chronic diseases in the CONSTANCES cohort

Justine Sauce, Sophie Ancelet, Corinne Mandin, Philippe Renaud, Jean-Michel Métivier, Abdulhamid Chaikh, Eric Blanchardon, David Broggio, Claire Greau, Caroline Vignaud, et al.

► To cite this version:

Justine Sauce, Sophie Ancelet, Corinne Mandin, Philippe Renaud, Jean-Michel Métivier, et al.. CORALE project: Cumulative lifetime multi-exposures to ionizing radiation and other risk factors and associations with chronic diseases in the CONSTANCES cohort. 10th Survival Analysis for Junior Researchers (SAfJR) Conference, Mar 2025, Bonn, Germany. . <hal-05023424>

HAL Id: hal-05023424

<https://hal.science/hal-05023424v1>

Submitted on 7 Apr 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License

CORALE PROJECT : CUMULATIVE LIFETIME MULTI-EXPOSURES TO IONIZING RADIATION AND OTHER RISK FACTORS AND ASSOCIATIONS WITH CHRONIC DISEASES IN THE CONSTANCES COHORT

J. Sauce^{1,2}, S. Ancelet¹, C. Mandin¹, P. Renaud³, J.-M. Métivier³, A. Chaikh¹, E. Blanchardon¹, D. Broggio¹, C. Gréau¹, C. Vignaud¹, M.-O. Bernier¹, E. Cléro¹, M. Goldberg⁴, C. Huet¹, S. Le Got⁴, E. Lequy^{4,5}, A. Isambert¹, A. M. S. Henyoh^{1,2}, G. Ielsch¹, C. Michel¹, C. Mukakalisa¹, M. Cœuret-Pellicer⁴, H. Roy¹, C. Ribet⁴, L. Saey³, M. Zins⁴, O. Laurent¹

¹ Autorité de Sécurité Nucléaire et de Radioprotection (ASNR), PSE-SANTE/SESANE/LEPID, PSE-SANTE/SER/UEM, PSE-ENV/SERPEN/BERAP, PSE-SANTE/SDOS/LEDI, PSE-ENV/SERPEN/BERAD, PSE-SANTE/SDOS/LDRIF, PSE-SANTE/SER/BASEP, F-92260 Fontenay-aux-Roses, France.

² Université Paris-Saclay, EDSP, F-94276 Villejuif, France.

³ Autorité de Sécurité Nucléaire et de Radioprotection (ASNR), PSE-ENV, PSE-ENV/SERPEN/LEREN, F-13115 Saint-Paul-Lez-Durance, France.

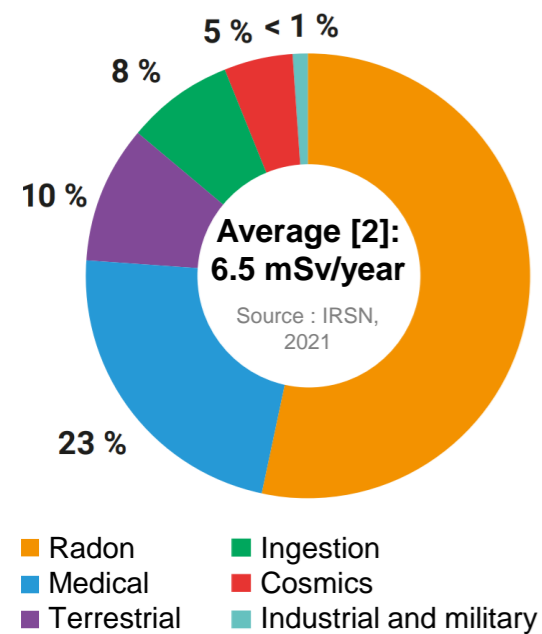
⁴ Université Paris Cité, Université Paris-Saclay, UVSQ, Inserm, Cohortes Epidémiologiques en population, UMS 11, Villejuif, France.

⁵ Université Paris-Saclay, UVSQ, Gustave Roussy, Inserm, CESP, Team "Exposome and Heredity", Villejuif, France

Introduction

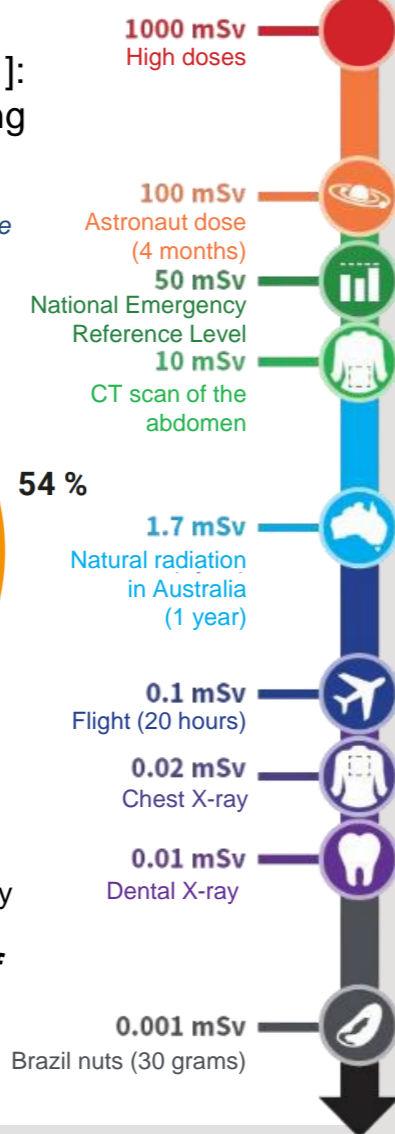
The radiological exposome [1]: cumulative exposure to ionizing radiation (IR) since conception.

Figure 1. Average annual effective dose of the French population, by sources [2]



What are the health effects of these cumulative lifetime exposures ?

Source : ARPANSA, 2021



Monte-Carlo simulations

Aim: to derive a quantification of the dose uncertainty associated with the accuracy of responses to the questionnaire.

Diagnostic nuclear medicine & CT-scans:

- Uncertain doses due to wide age/year at exposure range in questionnaire data before 2007

Air travel:

- Uncertainty on the number of flights
- Uncertainty on the type of destination

Cumulative dose estimates:

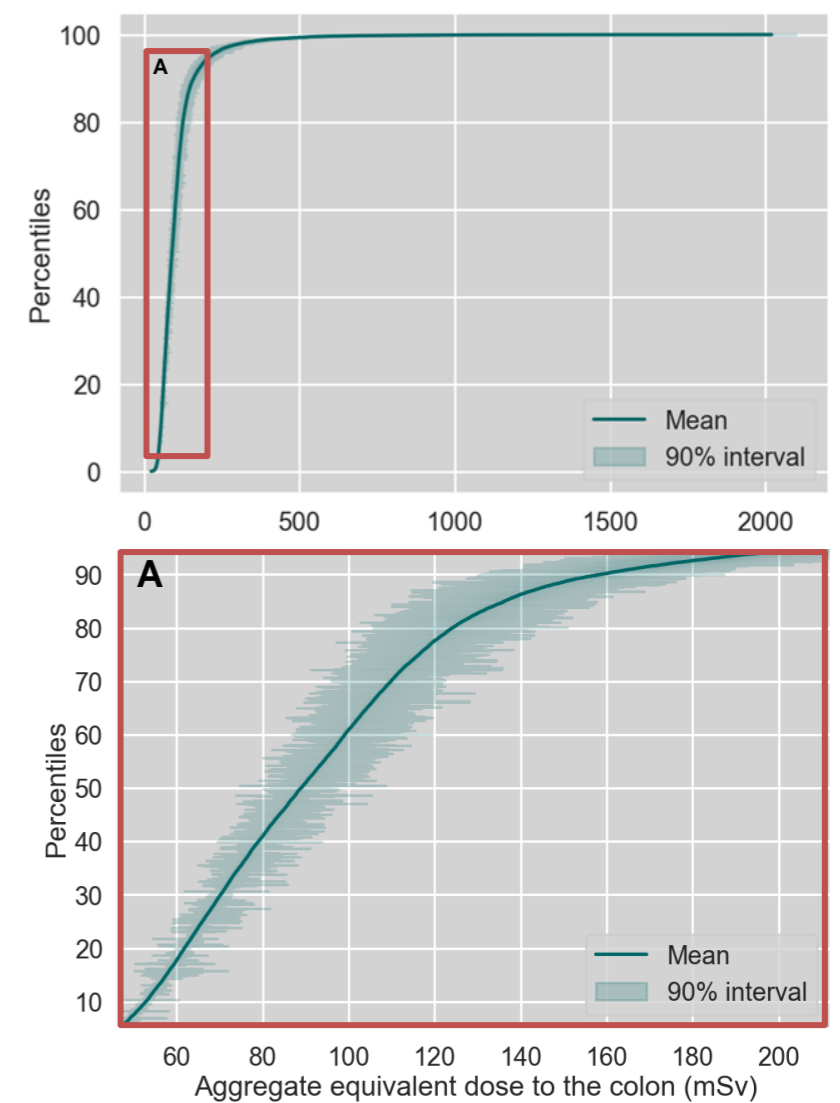
- For medical exposure simulations, the total average cumulative dose is expressed as follows:

$$D_{cumul,i} = \sum_{y=B}^{y=2006} D_{sim,i,y} + \sum_{y=2007}^{y=2020} D_{i,y} \quad (1)$$

where $D_{sim,i,y}$ (resp. $D_{i,y}$) is the average dose simulated (resp. dose non-simulated) for individual i and year y , and B is the birth year of participant i .

- 5th and 95th percentiles have been aggregated to produce a global 90% interval.

Figure 2. Cumulative distributions of aggregated colon dose (global view and rescaled 5th–95th percentiles view)



Objectives

- 01 Reconstruction of IR doses to 6 target organs from environmental and medical sources since birth, for about 40,000 participants.
- 02 Estimation of associations between lifetime doses of IR and chronic diseases, considering exposure to other risk factors.
- 03 Exploring potential associations between cancers and co-exposure to cumulative IR doses since birth and chemical pollutants (COREXCA project).

Material & Methods

Cohort: CONSTANCES general population cohort (managed by UMS 11 Inserm / UVSQ / U Paris Cité / U Paris-Saclay)

- Socio-demographic, lifestyle and medical history, including data from National Health Data System.
- Geocoded residential addresses for about 76,000 participants
- Questionnaire on IR : about 42,000 participants

Dosimetry methods [3]:

- Refined by year, age, sex and/or municipality, habits
- Organ doses estimated per year (from birth until 2020) and cumulated over a lifetime.

Statistical methods:

- Monte-Carlo (MC) simulations to estimate the average dose and its uncertainty linked to the questionnaire data
- Time-dependent Cox models [4]

Preliminary dosimetric results

Population study: 21,720 participants (with geocoded residential history covering the entire follow-up, and questionnaire data).

Figure 3. Cumulative average lifetime organ doses distribution from all sources

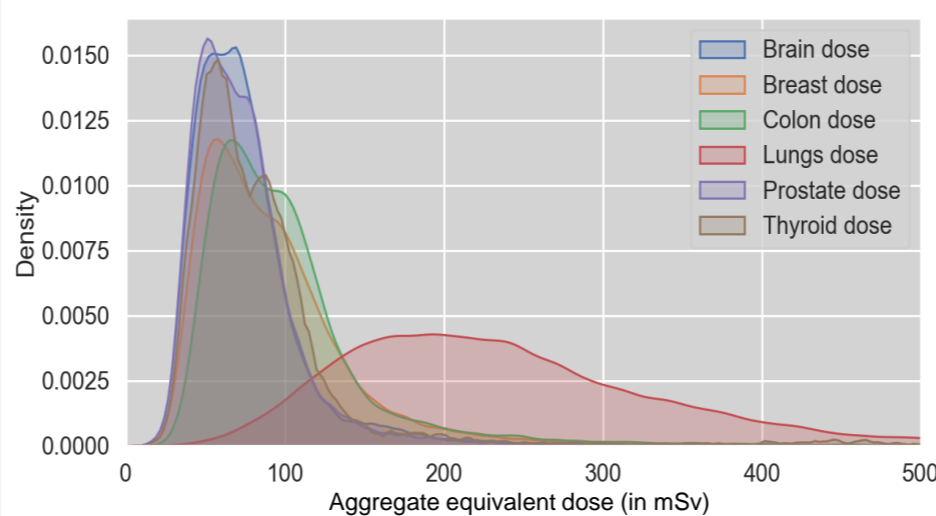
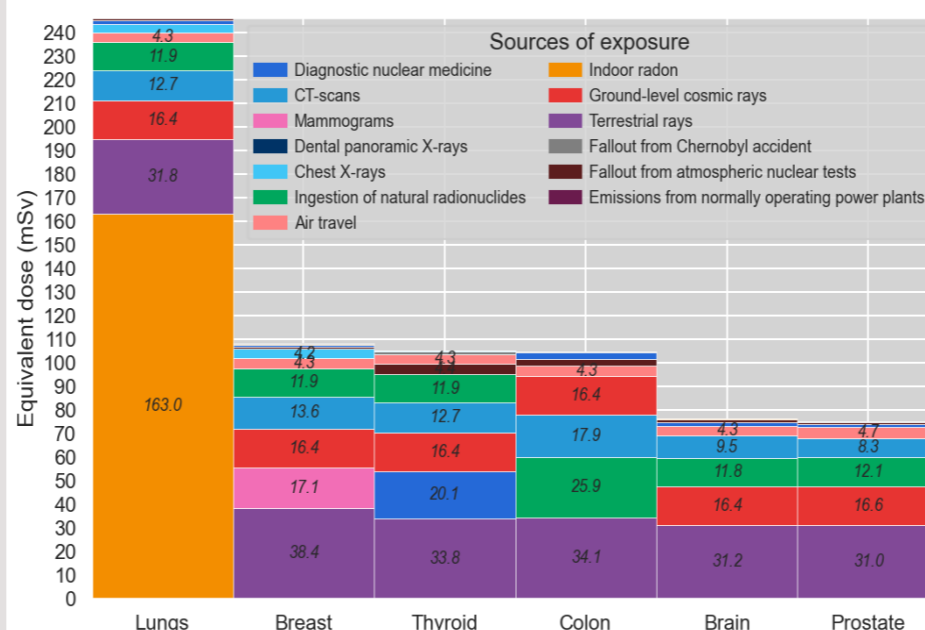


Figure 4. Cumulative average lifetime organ doses per source



Time-dependent Cox model

$$\lambda(t, X_i, Z_i) = \lambda_0(t) \exp\left(\sum_{k=1}^{p_i} \beta_k X_{ik}(t) + \gamma Z_i\right) \quad (2)$$

where $\lambda_0(t)$ is the baseline hazard function, $X_i(t)$ (resp. Z_i) is the time-varying (resp. time fixed) covariates, with p_i the number of longitudinal measures for each subject i ; β_k measures the association between longitudinal data and $\lambda(t)$, γ between time fixed covariates and $\lambda(t)$.

Results: Organ dose (cumulated per year with a 10-year lag) were associated with cancer incidence for breast (cases = 479), using attained age as time scale and adjusting for sex and decade of birth (HR for 100 mSv : 1.08, 95% CI [1.01;1.16]).

Discussion & Perspectives

Key elements: (on preliminary results)

- Significant uncertainty regarding the year of exposure (for some organs) from medical sources
- Cox models adjusted do not adequately account for the effect of organ dose on $\lambda(t)$ (log-linearity assumption does not hold in our study)
- Frequentist Cox models can be sensitive to errors and do not naturally take uncertainty into account

Perspectives:

- Inclusion of participants who responded to the questionnaire on paper (to date, only web responses have been processed)
- Quantifying uncertainties in organ dose estimates
- Hierarchical Bayesian regression models to consider uncertainties

References

- [1] Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev.* 2005 Aug; 14(8):1847-50
- [2] Institut de Radioprotection et de Sécurité Nucléaire. Exposition de la population française aux rayonnements ionisants. Bilan 2014-2019. IRSN; 2021. Report No.: IRSN 2021-00108.
- [3] Sauce J, et al. Reconstruction of the radiological component of the exposome in the CONSTANCES cohort. (currently being proofread).
- [4] Fisher LD, Lin DY. Time dependent covariates in the Cox proportional hazards regression model. *Annu Rev Public Health.* 1999;20(1):145-57.

Fundings: This project is partly funded by the Fondation de France (grant WB-2020-29711) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, grant EST-21-188 for COREXCA project)

