# 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.

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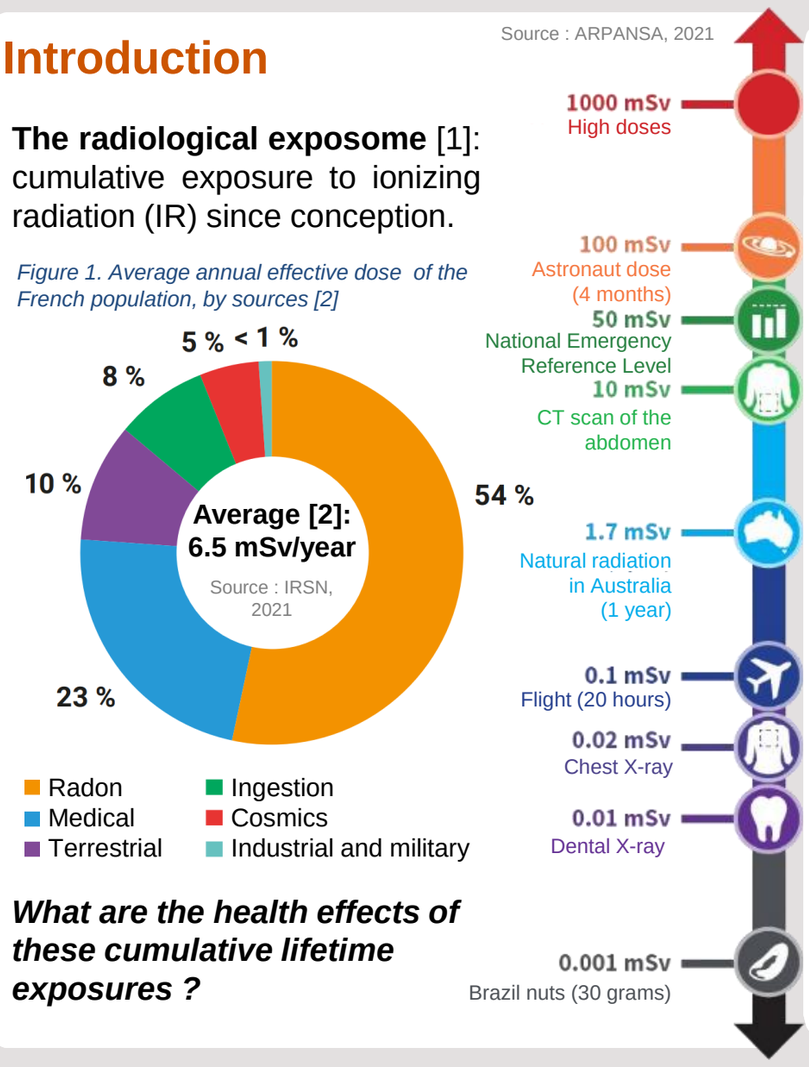
**J. Sauce**[1,2], S. Ancelet[1], C. Mandin[1], P. Renaud[3], J-M. Métivier[3], A. Chaikh[1], E. Blanchardon[1], D. Broggio[1], C. Gréau[1], C. Vignaud[1], M-O. Bernier[1], E. Cléro[1], M. Goldberg[4], C. Huet[1], S. Le Got[4], E. Lequy[4,5], A. Isambert[1], A. M. S. Henyoh[1,2], G. Ielsch[1], C. Michel[1], C. Mukakalisa[1], M. Cœuret-Pellicer[4], H. Roy[1], C. Ribet[4], L. Saey[3], M. Zins[4], O. Laurent[1]

[1] *Autorité de Sûreté 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 Sûreté 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 ?***

## 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

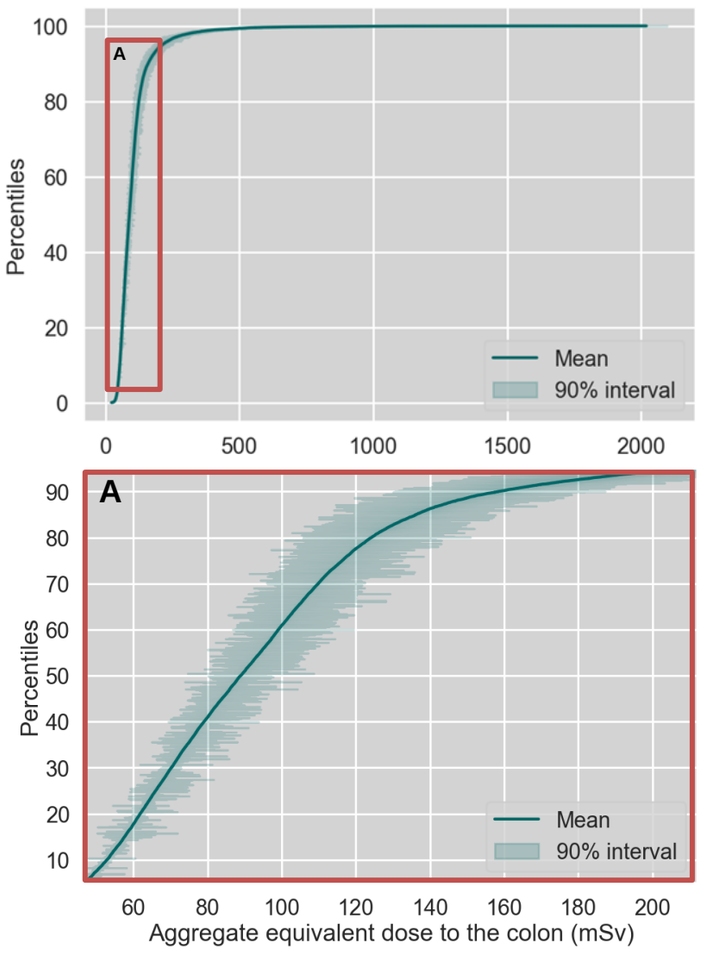
**Cumulative dose estimates**:
- For medical exposure simulations, the total average cumulative dose is expressed as follows:

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

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]

**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*

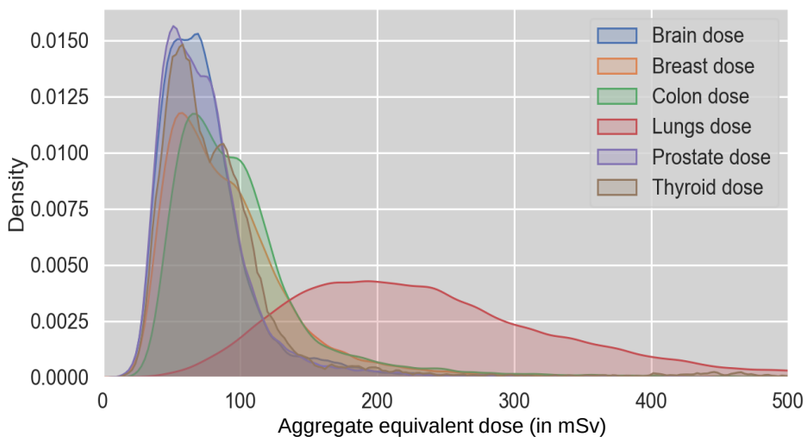
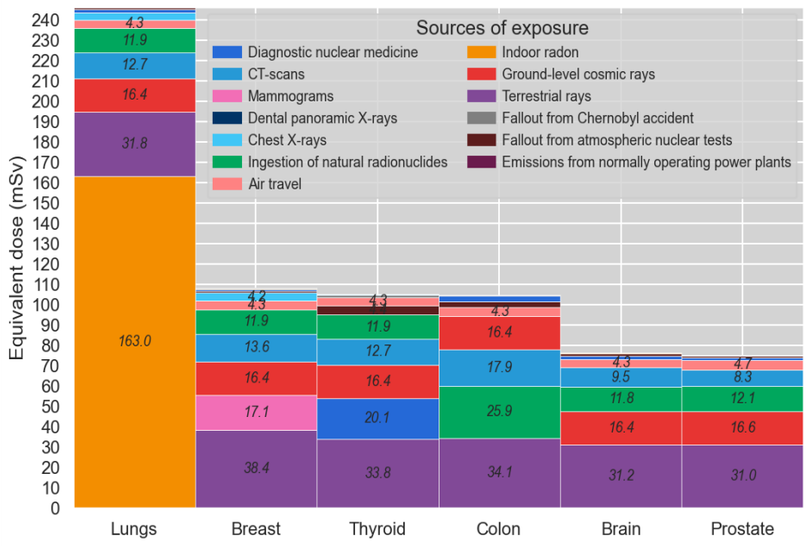



*Figure 4. Cumulative average lifetime organ doses per source*




## 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 $i$; $\beta_k$ measures the association between longitudinal data and $\lambda(t)$, $\gamma$ 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

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