Adult early-onset cancers: growing burden, increased risk, or expanded detection?

Study protocol for a PhD thesis

Date: 19 May 2025

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Background

Cancer is a major and growing public health burden worldwide [1–4], with approximately 20 million new cases and 10 million cancer deaths in 2022 [1]. In Switzerland, cancer was the leading cause of mortality among individuals aged 45 to 84 in 2023 [5]. The burden is primarily driven by population growth and aging, and will continue to increase as the population grows larger and older [1–4]. While the great majority of cancer occurs in people aged 50 and older [6], early-onset cancers, that is, diagnosed before the age of 50, have been reported to be on the rise in many countries [7–13].

Hence, between 1998 and 2012, in Europe, the cancer incidence rates increased among people aged 20-29 years old (annual percentage change (APC): +1.6%), 30-39 years old (APC: +1.0%) and 40-49 years old (APC: +0.4%) age groups [11]. Between 1995 and 2014, in the USA, the age-standardized incidence rates of multiple myeloma, leukemia, colorectal, uterine corpus, gallbladder, kidney, pancreas, and gastric non-cardia cancer increased at higher rates among people aged 24-49, compared to older adults, while the incidence of breast, ovary, lung and prostate cancers either decreased or stabilized [9]. Between 1996 and 2009 in Switzerland, the age-standardized incidence for breast cancer among women aged 20-49 years increased from 57/100’000 in 1996 to 68/100’000 in 2009 (APC: +0.8%) [14]. Worldwide, between 1990 and 2019, the number of cancer cases diagnosed from 14 to 49 years increased by 79% (1.82 million in 1990 to 3.26 million in 2019) and the number of related deaths by 28% (0.83 million in 1990 to 1.06 million in 2019) [7].

These trends and numbers attracted considerable media attention and raised public concern, urging for further research to tackle the underlying causes [15–18]. The potential causes of rising early-onset cancers include a combination of lifestyle, environmental, and detection-related factors [7–9,12,19–22]. The rising prevalence of obesity could be a crucial element as obesity is a known risk factor for several types of cancers including colorectal, kidney, liver, and pancreatic cancer [7–9,12,19–22]. Reproductive patterns such as delayed pregnancies and reduced breastfeeding contribute to a lesser extent on the risk of breast cancer [7–9,12,22] and environmental carcinogens, such as air pollution in some countries, are also suspected [7,8,21]. Detection-related factors might be key drivers of the increasing number of early-onset cancers [7–9,12,20–23]. Among these are advances in diagnostic tests sensitivity, increased physician supply, and broadened screening guidelines, which together may lead to earlier detection and increased screening among younger adults. More screening along with greater awareness of cancer risk and symptoms in the recent decades could result in wider diagnostic reach among people under 50 [24–26]. As a result, the increased incidence of early-onset cancers might not result from greater exposure to specific carcinogenic factors but could rather

reflect expanded detection practices. Deciphering which factors are at play can have an impact on cancer prevention strategies.

Breast cancer is one cancer whose incidence has increased in the last decades due notably to early diagnosis and screening [27]. While most cases are diagnosed after the age of 50 years, breast cancer is the most frequent cancer among young adults aged 14 to 49 years, accounting for 16.5% of all new cases worldwide in 2019 [7]. The burden of early-onset breast cancer could be driven by changes in diagnosis practices, including increased use of screening [28,29]. Accordingly, the U.S. Preventive Services Task Force (USPSTF) recently updated its recommendations to lower the starting age for screening from 50 to 40 years, highlighting the growing attention to earlier detection in younger women [25]. Shifts in guidelines might lead to breast cancer diagnosis at an earlier age and earlier stage, and ultimately might result in increased treatment by mastectomy in women younger than 50. Analyzing breast cancer trends by stages alongside mastectomy rates provides a comprehensive view of the burden of breast cancer among young women. Additionally, breast cancer trends by stages can reveal overdiagnosis, namely, the detection of a cancer that would have never caused symptoms in a woman's lifetime [27–32]. At the population-level, overdiagnosis is suspected when an increase in early-stages cancers is not matched by a corresponding decrease in advanced stages [32]. An additional proxy indicator of overdiagnosis could be provided by analyzing the mortality-to-incidence ratio (MIR), calculated by dividing the mortality rate by the incidence rate [33,34]. Studying breast cancer trends by stage and the MIR could be useful to determine to what extent overdiagnosis is one driver of the increasing rate of breast cancer among women younger than 50.

Regardless of the type of cancer, a major problem in the assessment of early-onset cancer trends, however, is the confusion between the absolute numbers of cases, the incidence rate, and the age-adjusted incidence rate. For instance, a study concluded that there was a global massive rise in early cancer cases and deaths after presenting absolute numbers without age adjustment, making it impossible to disentangle the effect of population growth and ageing from other factors [7]. In the appendix of the same study, the age-standardized incidence was reported to slightly increase from 76/100'000 in 1990 to 80/100'000 in 2019, corresponding to a relative rise of 5%, while the age-standardized mortality rate decreased from 35/100'000 to 26/100'000, corresponding to a relative decrease of 25%.

While absolute numbers and crude rates are valuable for reflecting the actual burden of cancer and for planning health services, they can contribute to the general misunderstanding when used to compare cancer statistics across different time periods. Because population ageing

and growth are the major drivers of cancer burden [3,4], it is crucial to report age-standardized rates when analyzing cancer trends over time [1,35]. Additionally, to study the specificity in the evolving burden of early-onset cancers and highlight any contrasting trends, it is also key to compare cancer trends between individuals under 50 years with later-onset cancer, i.e. among individuals aged 50 or older. While being diagnosed with cancer after the age of 50 has substantial repercussions, early-onset cancers might potentially bear distinct consequences such as reduced fertility and difficulties with career development at critical stages of adult life [36]. Identifying age-specific patterns of cancer is therefore crucial as the impact of the disease might differ between those diagnosed early and later in life.

For this PhD thesis, we aim to assess and understand some drivers of the long-term changes in the burden of adult early-onset cancers in Switzerland, in comparison to later-onset cancers, by studying 1) the burden of all cancer types, 2) the burden of breast cancer by stages and mastectomy rates, and 3) the trends in screening uptake and practices. We will conduct descriptive analysis on population-based data from cancer registries, hospital statistics, and health surveys [37].

Part 1 - Burden of adult early-onset cancer

Specific objectives

1.1) To describe the burden of adult early-onset cancers (20-49 years) of all cancer types, that is, the number of cases and deaths, and the crude and age-standardized incidence and mortality rates, compared to later-onset cancer (aged 50 or above), between 1982 and 2021 in Switzerland.

1.2) To describe age-standardized incidence and mortality of adult early-onset breast cancer by stages alongside mastectomy rates, in comparison with later-onset breast cancer between 1998 and 2021 in Switzerland. A secondary objective will be to assess the occurrence of overdiagnosis in early-onset breast cancer.

Methods

Study design and data source

1.1) We will conduct a population-based study using data from the Swiss National Institute for Cancer Epidemiology and Registration (NICER) [38].

1.2) We will conduct a population-based study using data from NICER and breast surgery data from the Hospital Medical Statistics by the Federal Statistical Office (FSO), which collects information on all Swiss inpatient cases [38,39].

Population and variables of interest

1.1) The target population for this study will be adults aged 20 years or older living in Switzerland. The study population will be the residential population covered by a cancer registry [40]. As not all cantons had a cancer registry before 2020, NICER estimated national cancer statistics from existing registries to extrapolate the expected data for areas not covered by a cancer registry. We will classify cancers by age at onset, defining *early-onset cancers* as those diagnosed in adults aged 20-49 years and *later-onset cancers* as those diagnosed at age 50 or older; for mortality analyses, we will correspondingly refer to deaths at ages 20-49 years as early mortality and later mortality for deaths at age 50 or older. We will include all cancer cases and deaths in people aged 20 years or older from January 1, 1982, to December 31, 2021, among residents in Switzerland. All cancer cases are coded using the 10th revision of the International Classification of Diseases (ICD-10). Before 1995, causes of deaths were coded using the 8th revision of the ICD and cancer was recorded as the cause of death whenever the term “tumor” appeared as either primary cause or as associated cause, unless conditions including accident, poisoning, trauma or flu were also listed on the death certificate [41]. As a result, cancer mortality rates prior to 1995 should be interpreted with caution as they might be overestimated. We will study, first, all types of cancer combined excluding non-melanoma skin cancer (C00-C97 excluding C44, ICD-10) and, second, specific types of cancer, including breast cancer (C50, ICD-10), prostate cancer (C61, ICD-10), lung/bronchus/trachea cancer (C33-34, ICD-10), colon-rectum cancer (C18-20, ICD-10), skin melanoma (C43, ICD-10) and, third, all other cancer sites combined and separately (C00-C97 except for C44, C50, C61, C33-34, C18-20, C43, ICD-10).

1.2) The target population will be women aged 20 years or older living in Switzerland. The study population will be the residential population covered by a cancer registry and women having been hospitalized in Switzerland [39,40]. We will classify breast cancer by age at onset, defining early-onset breast cancer as those diagnosed in adults aged 20-49 years and later-onset breast cancer as those diagnosed at age 50 or older; for mortality analyses, we will correspondingly refer to deaths at ages 20-49 years as early mortality and later mortality for deaths at age 50 or older. We will include all breast cancer cases (C50, ICD-10) diagnosed at 20 years or older from January 1, 1982, to December 31, 2021, among residents in Switzerland.

Statistical analysis

1.1) We will report the number of cases, crude incidence rate per 100’000 cases, age-standardized incidence rate per 100’000 cases (2013 European standard [42]), number of

deaths, crude mortality rate per 100'000 deaths, and age-standardized mortality rate per 100'000 deaths (2013 European standard [42]). We will estimate absolute annual mean change in rate per 100'000 and relative changes in the standardized rates using a linear regression model. We will also estimate annual percentage changes (APC) between two 5-year periods and average annual percentage change (AAPC) of age-standardized incidence and age-standardized mortality from the slope of the model. We will use the Joinpoint Regression Program, version 5.3.0 (National Cancer Institute), to identify and estimate the parameters of the linear model [43]. Analyses will be stratified by sex (men, women) and 5-year intervals age group at diagnosis (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, +95).

1.2) We will report the number of cases, crude incidence rate per 100'000 cases, age-standardized incidence rate per 100'000 cases (2013 European standard [42]), number of deaths, crude mortality rate per 100'000 deaths, age-standardized mortality rate per 100'000 deaths (2013 European standard [42]), age-standardized mastectomy rates per 100'000 breast cancers (2013 European standard [42]) and age-specific mortality-to-incidence ratio [33]. We will estimate the age-specific mortality-to-incidence ratio by dividing the age-specific mortality rates with age-specific incidence rates, based on the assumption that individuals within a given age group are part of the same birth cohort. We will estimate absolute annual mean change in rate per 100'000 and relative changes in the standardized rates using a linear regression model. We will also estimate APC of mastectomy from the slope of the model. We will use the Joinpoint Regression Program, version 5.3.0 (National Cancer Institute), to identify and estimate the parameters of the linear model [43]. Analyses will be stratified by 5-year intervals age group at diagnosis (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, +95 and breast cancer stages (0, I, II, III, IV).

Strengths and limitations

1.1) To our knowledge, this will be the first nationwide study studying the trends of all types of adult early-onset cancers over an extended period and comparing them with adult later-onset cancers. Analyses will be based on high-quality and population-based data from cancer registries. One limitation is the use of a cut-off at exactly 50 years, which might be arbitrary and lack clinical significance as the cut-off might be heterogeneous among the different types of adult early-onset cancer [22]. Furthermore, the study will be descriptive and will not study the causes for the changes in the burden beyond the effect of ageing and population growth.

1.2) Analyses will be based on high-quality and population-based data from cancer registries and hospital-based statistics. We will analyze breast cancer and mastectomy over the same

period to compare age-standardized incidence by stages, age-standardized mortality and mastectomy rates at the population level. These analyses could provide an estimation of overdiagnosis by looking at the difference between trends in early- and late-stages and at the mortality-to-incidence ratio. As mentioned in project 1.1, limitations will include the use of an arbitrary cut-off at exactly 50 years and the descriptive design of the study, which does not provide causes for the changes in the burden.

Part 2 - Cancer screening trends among adults under 50

Specific objective

To describe trends in cancer screening uptake and practices among adults before the age of 50 between 1992 and 2022 in Switzerland.

Methods

Study design and data source

We will conduct a population-based study using cancer data from the Swiss Health Survey, which is conducted by the FSO every five years (starting from 1992 to 2022) on a representative sample of individuals aged 15 years or older residing in Switzerland [38]. The Swiss Health Survey aims to assess the health and health-related behaviors of the Swiss population and uses a multistage randomized sampling method with stratification based on Swiss cantons. In the last wave of the Survey (2022), 60'651 Swiss residents aged 15 years or older were invited and 21'930 individuals agreed to participate in a telephone or in-person interview (participation rate of 36.2%).

Population and variables of interest

The target population for this study will be adults between 20 and 49 years of age living in Switzerland. The study population will be all participants of the Swiss Health Survey aged 20 or older starting from 1992 to 2022. Our analytical sample will include all participants after excluding proxy respondents who replied on behalf of someone else and participants with missing cancer screening data. We will study the cancer screening uptake (whether the individual has undergone any screening), the reason for undergoing the test (preventive, diagnostic, other), number of cancer screenings undergone (1, 2, 3, 4), type of cancer screening undergone (breast (mammography), cervical (cervix smear), colorectal (fecal occult blood test or colonoscopy), prostate (prostate specific antigen test or rectal exam), skin) and timing of last screening (up to 12 months, between 1 and 2 years, between 2 and 3 years, between 3 and 5 years, more than 5 years ago). Not all variables were available across all survey waves and all age groups. Some questions were introduced or modified in specific

waves (e.g. reason for undergoing the test) and some screening tests were restricted to specific age groups (e.g. prostate screening for men aged 40 and above).

Statistical analysis

We will estimate weighted proportions of the variables of interest stratified by year (every 5-year from 1992 to 2022), age (20-29, 30-39, 40-49, +50) and sex (men, women), using the weights provided by the Swiss Federal Office of Statistics [44]. The weights account for differences in demographic characteristics such as age, sex, region, nationality, civil status and household size, and non-response bias to make sure that results are representative of the Swiss population of 15 years and older [45].

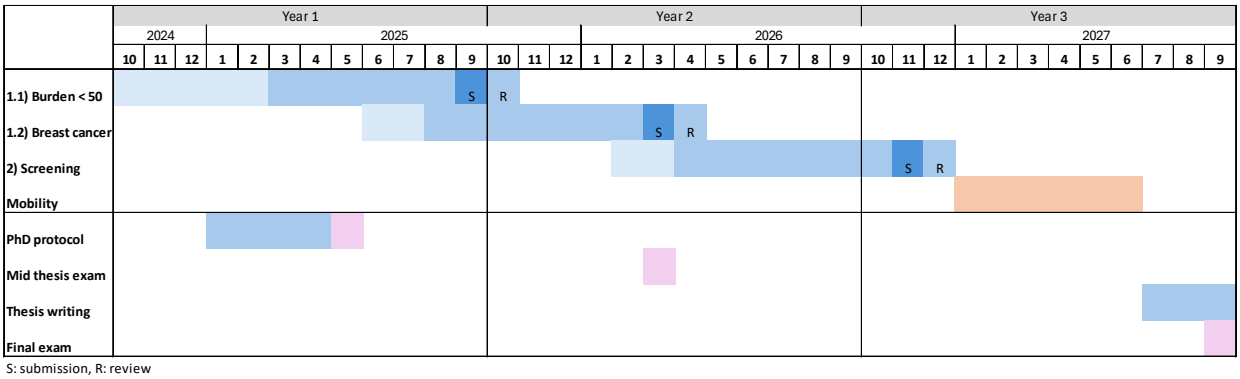
Strengths and limitations

Our study will provide an insight into how cancer screening among adults under 50 has evolved over the past decades. As most cancer screenings are not recommended before 50 in Switzerland [46], this study will explore the magnitude of screening outside recommendations. One limitation is the self-reported data collected through the Swiss Health Survey which could lead to information and misclassification biases.

Expected outcomes and public health impact of the PhD project

We will provide a comprehensive national overview of the trends of the cancer burden among people under the age of 50 with comparison to the cancer burden in those aged 50 and older. Identifying whether adult early-onset cancers are truly on the rise and whether this trend may indicate a genuine increasing risk or be influenced by changes in detection practices will provide useful information for healthcare providers and policymakers to assess whether targeted interventions (such as lowering the minimum age for screening) are needed. Additionally, clarifying key statistics in adult early-onset cancers epidemiology is essential and might help address confusion and public concern on this issue.

Estimated timeline



S: submission, R: review

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