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Is early-onset cancer an emerging global epidemic? Current evidence and future implications

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Abstract | Over the past several decades, the incidence of early-onset cancers, often defined as cancers diagnosed in adults <50 years of age, in the breast, colorectum, endometrium, oesophagus, extrahepatic bile duct, gallbladder, head and neck, kidney, liver, bone marrow, pancreas, prostate, stomach and thyroid has increased in multiple countries. Increased use of screening programmes has contributed to this phenomenon to a certain extent, although a genuine increase in the incidence of early-onset forms of several cancer types also seems to have emerged. Evidence suggests an aetiological role of risk factor exposures in early life and young adulthood. Since the mid-20th century, substantial multigenerational changes in the exposome have occurred (including changes in diet, lifestyle, obesity, environment and the microbiome, all of which might interact with genomic and/or genetic susceptibilities). However, the effects of individual exposures remain largely unknown. To study early-life exposures and their implications for multiple cancer types will require prospective cohort studies with dedicated biobanking and data collection technologies. Raising awareness among both the public and health-care professionals will also be critical. In this Review, we describe changes in the incidence of early-onset cancers globally and suggest measures that are likely to reduce the burden of cancers and other chronic non-communicable diseases.

Cancer is a multifactorial disease that most commonly affects people ≥50 years of age. However, evidence indicates that the incidence of cancers of various organs (including those of the breast, colorectum, endometrium, oesophagus, extrahepatic bile duct, gallbladder, head and neck, kidney, liver, bone marrow (multiple myeloma (MM)), pancreas, prostate, stomach and thyroid) has been rising in adults <50 years of age in many parts of the world[1–13]. This trend is also observed in analyses using Global Cancer Observatory (GLOBOCAN; https://gco.iarc.fr/) data (FIG. 1 provides data on selected countries; more comprehensive data are provided in Supplementary Table 1). We herein use the term ‘early-onset’ to describe cancers diagnosed in adults <50 years of age, and a contrasting term, ‘later-onset’, for cancers diagnosed in those ≥50 years of age. Cancers diagnosed during childhood and adolescence (<20 years of age) are out of the scope of this Review.

The rise of early-onset cancer has considerable personal, societal and economic implications. Survivors of early-onset cancers have a higher risk of long-term health problems such as infertility, cardiovascular disease and secondary cancers[14–16]. Owing to this increasing cancer burden among young adults, which might be referred to as the ‘early-onset cancer epidemic’, the US National Cancer Institute listed this phenomenon as a research priority in one of its ‘Provocative Questions’ for 2020–2021 (REF.[17]).

Differences in epidemiology and clinical, pathological, and molecular characteristics clearly exist between early-onset and later-onset cancers, although these features are not likely to change dramatically at exactly 50 years of age[18]. Furthermore, early-onset cancer in any given organ is not a homogeneous entity but rather encompasses a variable range of clinical and pathological features[18,19]. We acknowledge the limitations of applying a dichotomy at 50 years of age, although we selected this cut-off point to enable consistent collection and interpretation of current evidence on early-onset cancers. In reality, we also need to consider heterogeneity within

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Key points

- The incidence of cancers of various organs diagnosed in adults ≤50 years of age has been rising in many parts of the world since the 1990s.
- Evidence suggests an aetiological role for risk factor exposures in early life and young adulthood, although specific effects of individual exposures remain largely unknown.
- The early life exposome (including, among other factors, diet, lifestyle, obesity, environmental exposures and the microbiome) has changed substantially, with variable trends observed around the world since the mid-20th century.
- The early-onset cancer epidemic might be one manifestation of increasing trends in the development of many chronic diseases in young and future generations.
- Prospective cohort studies using electronic health records and/or early-life biospecimen collection would enable the detailed investigation of early-life factors in relation to many future health outcomes, including cancer.
- Raising awareness of the early-onset cancer epidemic and improving the early-life environment should be our immediate goals: these are likely to reduce the burden of both early-onset and later-onset cancers.

this group. In addition, considering the variable distribution of age at cancer diagnosis by different organ sites, the optimal screening and treatment options for various age groups should be studied according to organ site.

In this Review, we evaluate and summarize evidence on the pertinent features and possible risk-factor profiles of early-onset forms of cancer types with an increased incidence reported over the past decades. In-depth investigations of putative risk factors and tumour molecular characteristics across multiple early-onset cancer types could shed light on plausible common aetiologies. Improved knowledge of pathogenesis can also inform strategies for primary prevention, early detection and treatment. We also discuss strategies to address research gaps and promote prevention efforts, which have broader public health implications. We use the standardized nomenclature system for genes and gene products designated by the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC) along with colloquial names, to reduce ambiguity and increase clarity[20].

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Current evidence

Risk factors in early life and young adulthood. The rising incidence of early-onset cancers is probably partially attributable to increasing uptake of screening and early detection before the age of 50 years, to variable degrees across certain cancer types, especially breast, prostate and thyroid cancers. However, increasing incidence of early-onset cancers in several organs, such as colorectal and pancreatic cancers, which might not be fully explained by screening is also apparent. This trend could reflect increased risk factor exposures in early life and/or young adulthood[18]. In this Review the term 'early life', is broadly defined as conception to the end of adolescence (19 years of age), and the contrasting term 'adulthood' is applied thereafter. Accumulating evidence suggests that the earliest phase of carcinogenesis might start in early life or young adulthood[18,21], followed by intervals of up to several decades between initial cellular damage and clinical cancer detection[22,23]. Even in utero exposures can lead to cellular reprogramming, including epigenetic alterations, that might have long-lasting effects on susceptibility to chronic diseases[24–26]. For example, data from the Dutch Famine Birth Cohort indicate that prenatal food restriction is associated with increased long-term risks of certain health conditions, including coronary heart disease and breast cancer, among adults[27,28]. Similarly, data from the Child Health and Development Studies suggest that maternal obesity increases the risk of colorectal cancer (CRC) in offspring[29]. Data from another study indicate a positive association between birthweight and colon cancer risk in adulthood[30]. Exposure to ionizing radiation and age at menarche are other factors occurring in childhood or young adulthood that can affect disease risk in later life[31,32]. These observations underscore the aetiological role of early-life exposures in cancer development.

Another aetiological insight into the rise of early-onset cancers can be derived from trends in CRC incidence in the USA; the incidence of later-onset CRC (in those born in the late 19th and early 20th centuries) started to increase in the 1950s whereas that of early-onset CRC (in those born in the mid-20th century) did not start to increase until the early 1990s[33,34]. Similar trends have been observed in other countries, including New Zealand, Australia and Canada[35]. This time lag suggests that risk factor exposures, which started increasing similarly across broad age groups around the 1940s to 1950s and continued increasing for decades, might affect cancer risk in older individuals sooner than in younger individuals, in whom the increase in cancer incidence appeared several decades later[18]. Considering this time lag between increases in

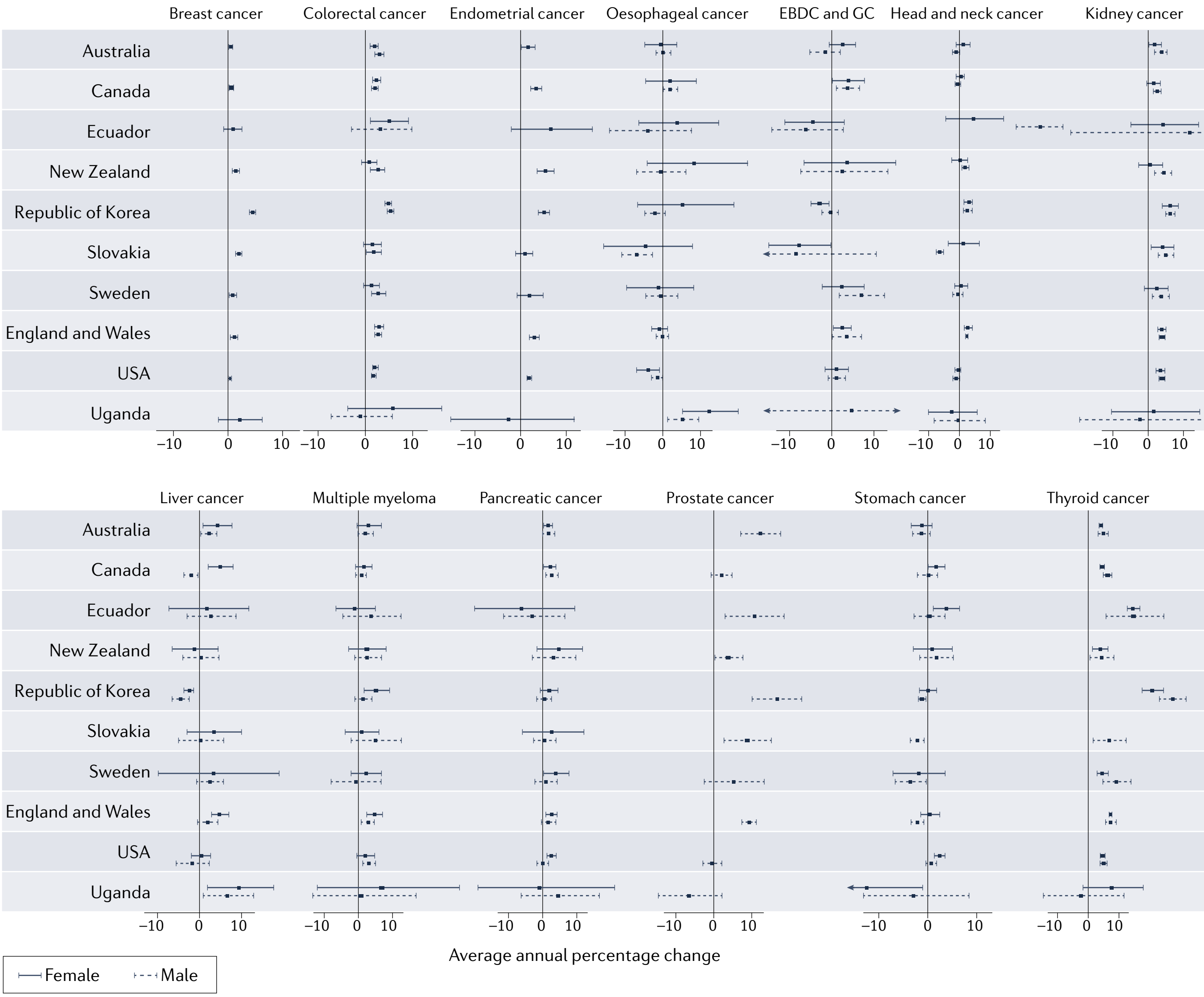

Fig. 1 | **Trends in incidence of selected early-onset cancers.** Trends in the incidence of 14 cancer types with increasing incidences among 20–49-year-old adults between 2002 and 2012 by country and region. Age-standardized cancer incidence data were obtained from the Global Cancer Observatory (GLOBOCAN; https://gco.iarc.fr/). Horizontal bars indicate 95% CIs. Larger 95% CIs that do not fit onto the graph scale are indicated by arrows. Data were obtained from 44 countries that provided age-standardized data on cancer incidence for the period 2002–2012. From among these, we selected ten countries that are indicative of trends in specific geographical regions. The full dataset, including data from all 44 countries, is shown in Supplementary Table 1. Average annual percentage changes with 95% CIs (shown as horizontal bars) in incidence were calculated using the Joinpoint Regression Program (version 4.9.0.1) for data obtained for the period 2002–2012, except for Slovakia (2000–2010) owing to differences in data availability. A maximum of two joinpoints were permitted in this analysis. Although extrahepatic bile duct cancer and gallbladder cancer (EBDC and GC) are distinct cancer types, making precise classifications is often difficult; hence, these cancer types are often recorded and data calculated together. Data were not available on the incidence of thyroid cancer among women in Slovakia.

the incidence of later-onset and early-onset CRCs, further investigation of dietary, lifestyle and environmental exposures (including less-studied exposures) that have increased since the 1940s to 1950s is warranted. Many older individuals might have already accumulated cellular alterations (and/or developed premalignant lesions), which led to an increased incidence of cancer within relatively short periods after factors such as the westernization of diet and lifestyle started spreading in the mid-20th century. By contrast, such (then early-life) exposures might have taken decades to increase the incidence of cancer in younger individuals who are likely to have accumulated fewer potentially detrimental cellular alterations. Data from successive birth cohorts since the mid-20th century have demonstrated increased incidence of cancers of the colorectum, endometrium, oesophagus, gallbladder, extrahepatic bile duct, kidney, thyroid and bone marrow (MM)[8,36]. This so-called birth cohort effect suggests an important role for early-life risk factor exposures for the observed increase in the incidence of early-onset cancers.

The early-onset cancer epidemic is probably attributable to changes in patterns of exposure in early life and/or young adulthood, although comprehensive analyses of individual risk factors in these early life stages remain limited. The possible long latency of exposure effects poses certain challenges. For example, unhealthy dietary components and other detrimental lifestyle behaviours are often correlated, making it difficult to disentangle confounding and estimate the true effect size of each individual risk factor. Confounding can also involve exposures at different stages of life. A childhood exposure (such as obesity[37,38]) that is causally associated with an adulthood exposure (in this example, obesity again) can become a confounder for the adulthood exposure. If such confounding exists, it becomes challenging to form accurate conclusions on the causality of the adulthood exposure unless the confounder can be accurately measured and analysed.

Temporal trends in exposures. In parallel with the global trends towards more-westernized diets, lifestyles and environments, the exposome (meaning the totality of exposures including, among others, diet, lifestyle, environment and the microbiota) during early life and young adulthood has changed substantially, albeit with large geographical variations, since the mid-20th century[8,18,21,39]. Temporal trends in putative risk factors since the mid-20th century (BOX 1,2) might have affected the incidence of early-onset cancer, starting from the 1990s. Briefly, trends have emerged towards increasing height[40], overweight and obesity[41,42], type 2 diabetes[43–46], physical inactivity[47–49], western-style diet (defined as a diet high in saturated fats, red meat, processed meat, sugar and ultra-processed foods, but low in fruits, vegetables, whole grains and fibre)[50–56], and sugar-sweetened beverage intake[55,57,58] in children, adolescents and adults worldwide (FIG. 2). Per capita alcohol consumption also generally increased between 1960 and 2010, albeit with considerable variations between countries[59–63]. Smoking habits have also changed in various ways during different time periods in different countries[64–69]. In addition to personal smoking habits, effects of involuntary (second-hand or in utero) smoke exposure especially during (but not limited to) early life might not be trivial. Sleep patterns as well as the extent of exposure to bright lights at night have also changed in children, adolescents and adults since the early 20th century[70–72]. Reproductive factor exposures apply mostly to parents, especially mothers, although certain factors apply to both parents and offspring. Age at menarche and the overall number of births have decreased[73–77], whereas age at both first and last birth, and oral contraceptive use have increased[78,79]. More widespread use of infant formula led to a global decline in breastfeeding in the 20th century[80]. Nonetheless, a trend towards increased breastfeeding has emerged in high-income countries since the 1990s[81].

In addition to reproductive factors, smoking, diet, alcohol consumption, lifestyle and morbidities during pregnancy might all be relevant in utero exposures. These might affect the risk of cancers in variable target organs with different latency periods in mothers relative to offspring. Similarly, non-linear time-varying changes in exposures involving both mother and offspring (such as breastfeeding and/or infant formula intake) in the past century might have influenced the incidence trends for various cancer types differentially in both mothers and offspring.

Notably, influences of any of these exposure trends in early life and young adulthood on cancer incidence are unlikely to appear until decades later. Therefore, a declining (or non-increasing) trend of a given risk factor in the past few decades (such as since the 1990s) does not imply that early-life exposure to that factor is not one of the causes of the early-onset cancer epidemic. This premise might hold true for early-life exposure to smoking, alcohol, or chronic hepatitis B virus (HBV), human papillomavirus (HPV), or *Helicobacter pylori* infections in certain countries. Data on exposure trends over the past several decades might be useful to predict future trends in cancer incidence across various age groups if we can elucidate their aetiological roles.

Other factors. The microbiome is another notable contributor to tumour development[82]. Among the 14 early-onset cancer types with a rising incidence, eight (those of the colorectum, oesophagus, extrahepatic bile duct, gallbladder, head and neck, liver, pancreas and stomach) relate to the digestive system, indicating the potential pathogenic importance of both the oral and intestinal microbiome. Nutrition, lifestyle factors and antibiotic use can all influence the development of various chronic diseases through various physiological mechanisms, including microbial alterations[82–84]. Antibiotic use, which has been associated with certain cancer types[85], has increased in both adults and children in many countries over the past half century[86–88]. Inflammatory bowel disease (an established risk factor for CRC), in which the microbiome has a major pathogenic role, has increased in adolescents since the 1980s[89,90]. The early-life microbiome is known to influence the development of the immune system[91,92]. Therefore, tumour–microbial–immune interactions are an emerging research frontier[93], which will probably provide novel aetiological insights.

Interestingly, a polygenic risk score based on many low-penetrance variants is more strongly associated with early-onset CRC than later-onset CRC[94]. Similar phenomena have been observed for breast and prostate cancers[95,96]. Certain environmental and/or lifestyle risk factors occurring in early life to young adulthood might make individuals carrying a higher number of low-penetrance risk variants more susceptible to cancer development.

Germline genetic variations in certain hereditary cancer-related genes are associated with early-onset cancers[97–99]. Owing to advances in medicine over the past decades, individuals carrying certain high-penetrance variants (that would have tended to be removed from the population pool without advances in medicine) have increasingly had the chance to reproduce and therefore pass their variants to the next generation. This effect might be causing an increase in the population prevalence of high-penetrance variants of certain genes. However, multiple generations would probably be required to enable the detection of observable differences in the prevalence of such variants. Despite this speculation, thus far, no evidence for increased population prevalence of high-penetrance variants in any gene has emerged. Furthermore, at least another few

Box 1 | **Overall and/or adult temporal trends in exposures[a]**

Alcohol

- **Overall**
  - Per capita alcohol (ethanol) consumption among individuals of any age increased from the 1960s to early 2010s in many countries[59].
  - A decline in alcohol consumption was seen in Western Europe, whereas alcohol consumption increased in Eastern Europe, Asia and Middle Eastern countries during this period[59].
  - The ratio of male to female drinkers decreased in the Western Pacific region from 1990 to 2017, owing to an increase in the number of female drinkers[335].

Antibiotics

- **Overall**
  - Global per-capita consumption of antibiotics increased during 2000–2015 (REF.[85]).

Height

- **Overall**
  - Approximately 0.1 cm increase in average adult height (per 1 year increase in birth year) throughout the 20th century in the populations of several European countries[40].
  - Approximately 0.2 cm increase in average adult height (per 1 year increase in birth year) in the latter half of the 20th century in the population of South Korea[40].

Obesity

- **Adults**
  - Global age-standardized prevalence of obesity (BMI ≥30 kg/m^2) increased from 3.2% to 10.8% in men, and from 6.4% to 14.9% in women during 1975–2014 (REF.[41]).

Physical inactivity and sedentary lifestyle

- **Adults**
  - Occupational physical activity generally decreased while leisure-time physical activity generally increased or remained stable during the 1980s–2000s[48].
  - Average sitting time increased from 7.0 to 8.2 hours/day during 2007–2016 (REF.[49]).

Reproductive factors

- **Overall**
  - Average age at menarche globally declined with greater declines in low/middle-income countries compared with high-income countries[73]. Data from a UK-based study indicate that average age at menarche changed from 13.5 years of age in women born between 1908–1919 to 12.3 years of age in women born between 1990–1993 (REF.[74]).
  - Average age at first birth increased by 2–5 years during 1970–2018 in all OECD countries with available data[77].
  - Global fertility rate decreased from 5.0 births per women over a lifetime in 1950 to 2.5 in 2022 (REF.[75]).
  - The fertility rate decreased from 3.7 births per women over a lifetime in 1960 to 1.6 in 2020, and consequently the prevalence of women who never breastfed increased during the same period in the USA[73].
  - Global use of oral contraception increased from <40% to 60% of women 15–49 years of age during 1960s– 2009 (REF.[78]).
  - Increasing use of infant formula in the 20th century led to a global decline in breastfeeding[79]. Since the 1990s, high-income countries have generally shown an increase in exclusive breastfeeding rates (average rate: 25% in 1993 to 36% in 2014)[80].

Sleep duration and pattern changes (such as night shift work)

- **Adults**
  - Reported sleep duration in adults has not changed significantly during 1960–2013 according to a systematic review of reports from Australia, Finland, Italy, Ireland, Japan, New Zealand, UK and the USA[71].
  - The prevalence of night shift workers has changed over the past few decades in Australia, Canada, China, Europe, Japan, South America and the USA[72].

Smoking

- **Adults**
  - Smoking prevalence in men >20 years of age has decreased continuously in the USA, Canada, UK, Norway and Sweden during 1974–1987 (REF.[64]).
  - Smoking prevalence in women aged >20 years showed a slight fluctuation during the same period albeit with a general trend towards a decreasing prevalence (with the exception of Norway)[64].
  - In the Netherlands, UK, Ireland and Denmark, smoking prevalence decreased continuously in men aged >15 years during 1950–1990, but increased in women aged >15 years during the mid-1960s–1980s[65].
  - In China (urban areas), smoking prevalence increased in successive birth cohorts of men born in the 1920s to those born in the 1950s or later, whereas, in India, Japan, Singapore, South Korea and Taiwan, smoking prevalence plateaued in men born during the same period[68].
  - Smoking prevalence remained low in women born during the same period in these Asian countries[68].
  - The age-standardized prevalence of smoking has increased since 1990 in Africa and since 2010 in Latin America[69].
  - Adult smoking is directly linked with early-life involuntary smoke (secondhand or in utero) exposure in offspring.

Type 2 diabetes mellitus

- **Overall**
  - The global age-standardized incidence rate of type 2 diabetes mellitus per 100,000 per year increased from 229 (95% CI 214–244) in 1990 to 279 (95% CI 257–304) in 2017 (REF.[43]).
  - Mean age at a new diagnosis of type 2 diabetes declined from 52 in 1988–1994 to 46 in 1999–2000 in the USA[44].

Western-style diet and sweetened beverage consumption

- **Overall**
  - Western-style diet (a diet high in saturated fats, red meat, processed meat, sugar and processed food, but low in fruits, vegetables, whole grains and fibre) has spread worldwide in all age groups over the past 50 years[50–54].
  - Consumption of sugar-sweetened beverages has increased globally from 2000 to 2013 (REF.[55]).

BMI, body mass index; CI, confidence interval; OECD, Organization for Economic Co-operation and Development.

[a]Several decades will likely be required in order to observe possible effects of early-life exposures on the incidence of early-onset cancers. Hence, effects of a temporal trend associated with a specific early-life exposure in the past few decades are unlikely to have appeared in the literature on early-onset cancer incidence.

decades would be required to observe an increased incidence of early-onset cancer in adults owing to an increase in the prevalence of high-penetrance variants (if it exists). The implications of an as-yet unobserved but seemingly plausible increase in the prevalence of certain high-penetrance variants in the population will be an issue to be addressed in the future.

Organ-specific considerations

Evidence regarding risk factors has emerged for several early-onset cancers (TABLE 1; details in Supplementary Tables 2–12). Pertinent findings for each cancer type are summarized below. Many studies are reliant on small sample sizes and most of the results presented require replication.

Breast cancer. Here we discuss premenopausal breast cancer, as studies have typically divided women with breast cancer cases based on their menopausal status at diagnosis (instead of applying an exact age cut-off). Menopause most commonly occurs between the ages of 45 and 55 years worldwide[100].

Enhanced screening and detection have probably contributed to an increased incidence of premenopausal breast cancer in countries with certain screening programmes, albeit to an unknown extent. Mammography screening became increasingly prevalent worldwide between 2005 and 2015 (REF.[101]). In the USA, although the age at which screening is initiated has changed over time since the introduction of mammography screening in the 1980s[102,103], the incidence of breast cancer has increased most prominently in women <40 years of age, who are below the routine screening age[104]. The incidence of premenopausal breast cancer has also increased in countries that do not have routine screening programmes[105].

Reproductive factors including younger age at menarche[106–109], oral contraceptive use[109,110], nulliparity[106,109], older age at first birth[106,109,111] and never-breastfeeding[106] are established risk factors for premenopausal breast cancer. Interestingly, trend analyses suggest that declining trends in fertility rates together with increasing trends in additional risk factor exposures since the 1930s might have contributed to the increased incidence of premenopausal breast cancer[105,112,113]. Data also show that premenopausal breast cancer risk is reduced by a higher adulthood BMI and weight at age 18 years[114–120], but is increased by height, waist to hip ratio and weight gain in older adulthood[115,121–123]. The underlying mechanisms of these various relationships remain unclear.

A meta-analysis published in 2019 found an inverse association between vigorous physical activity and premenopausal breast cancer risk[124]. Alcohol consumption is also a risk factor for premenopausal breast cancer[125–128]. Another meta-analysis did not find a statistically significant association between a western diet and premenopausal breast cancer risk[129], although data from several studies suggest that greater fat intake during adolescence and animal fat intake during young adulthood are associated with increased premenopausal breast cancer risk[130,131]. Data from several studies suggest an increased risk of premenopausal breast cancer among smokers, with a prolonged latency period[132–135].

Most premenopausal breast cancers arise sporadically, although a minority are hereditary and are caused by the presence of high-penetrance genetic variants (such as loss-of-function mutations in *BRCA1* and *BRCA2*)[97,136]. In one study, 12% of patients with breast cancer diagnosed at ≤40 years of age had germline mutations in *BRCA1* or *BRCA2* (REF.[137]). Data from

Box 2 | **Temporal trends in exposures in adolescents and/or children[a]**

Alcohol

- **Adolescents**
  - The prevalence of binge drinking (defined as having more than four drinks in a row at least once in the past 2 weeks) among 12th-grade students in the USA peaked in 1979 and then declined from 41% in 1983 to 28% in 1992 (REF.[60]).
  - The National Survey on Drug Use and Health reported a consistent decline in the prevalence of alcohol consumption from 10.5% to 2.7% among adolescents 12–14 years of age and from 30% to 16% among those 15–17 years of age during 1991 to 2019 (REF.[61]).
  - Underage drinking has decreased in most high-income countries, but also increased in Argentina, Benin, Mexico, Myanmar, Thailand, Vanuatu between 2007–2009 to 2014–2016 (REFS.[62,63]).

Antibiotics

- **Children**
  - Antibiotic use among children (<15 years of age) increased during 1980–1992 in the USA[87].
  - Global antibiotic consumption among children (<5 years of age) increased from 9.8 (defined daily doses per 1,000 population per day) in 2000 to 14.3 in 2018 (REF.[86]).

Obesity

- **Children and/or adolescents (5–19 years of age)**
  - Global age-standardized prevalence of obesity in children and adolescents 5–19 years of age increased from 0.7% to 5.6% in girls and from 0.9% to 7.8% in boys during 1975–2016 (REF.[41]).

Physical inactivity and sedentary lifestyle

- **Children and/or adolescents**
  - Physical activity generally decreased among children and adolescents[48].
  - Average sitting time increased from 5.5 to 6.4 hours/day during 2007–2016 (REF.[49]).

Sleep duration and pattern changes (such as night shift work)

- **Children and/or adolescents**
  - Reported sleep durations of children and adolescents have declined by >60 min per night during 1905–2008 according to a systematic review of reports from 20 countries in Asia, Europe, North America and Oceania[70].

Smoking

- **Adolescents (age 12–20 years)**
  - The global prevalence of smoking among adolescents 13–15 years of age decreased from 1999–2018 (REF.[334]).
  - The prevalence of cigarette smoking decreased among adolescents 12–16 years of age during 1974 to 1991 in the USA[66].
  - Smoking initiation rate during early (11–15 years of age) and late adolescence (16–20 years of age) declined for both men and women in most European countries during the 1970s–1980s[67].

Type 2 diabetes mellitus

- **Children and/or adolescents (<20 years of age)**
  - Incidence rate per 100,000 youths <20 years of age per year in the USA increased from 9.0 to 12.5 during 2003–2012 (REF.[45]).
  - The global incidence of type 2 diabetes varies substantially among countries, age categories, and ethnic groups, but has increased in most areas in the past few decades[46].

Western-style diet and sweetened beverage consumption

- **Children and/or adolescents**
  - Both high-income countries (including the USA) and low-income countries have seen an increase in the consumption of sweetened beverages among children and adolescents since the 1980s[57,58].
  - Increasing early-life calorie/food intake might have led to an increase in average height between 1896–1996 in 200 countries, although this trend varies by country[56].

[a]Several decades will probably be required in order to observe possible effects of early-life exposures on the incidence of early-onset cancers. Hence, effects of a temporal trend associated with a specific early-life exposure in the past few decades are unlikely to have appeared in the literature on early-onset cancer incidence.

other studies indicate that 5% of patients with breast cancer diagnosed at ≤35 years of age have germline *TP53* mutations and 1% of those ≤40 years of age have germline *PALB2* mutations[138,139]. In addition, many low-penetrance genetic variants are associated with breast cancer risk[140]. However, none of these studies provided strong evidence for a role of gene–environment interactions in premenopausal breast cancer risk[141,142].

On the basis of current evidence, the trend of reproductive factors, central obesity, physical inactivity, alcohol consumption and dietary westernization since the mid-20th century might have contributed to the rising incidence of premenopausal breast cancer. Evidence also indicates differences in tumour molecular subtype distribution between premenopausal and postmenopausal breast cancers[143]. Compared to women with postmenopausal breast cancer, those with premenopausal disease are more likely to have breast cancers of an ESR1 (also known as ER)-negative or triple-negative (ESR1-negative, PGR (also known as PR)-negative, ERBB2 (also known as HER2)-negative) subtype[144]. In the USA, Black women tend to be diagnosed with breast cancer at an earlier age than women from other ethnic groups[145]. Therefore, unidentified risk factors for certain breast cancer subtypes or specific populations might contribute to the observed increasing incidence of premenopausal breast cancer.

Colorectal cancer. Data from previous studies have linked high adulthood BMI with early-onset CRC[146–155], and a few studies have demonstrated an association between BMI during childhood or adolescence with early-onset CRC[146,156]. The association of adolescence or young adulthood obesity with early-onset CRC has been reported to be either stronger[149–152] or weaker[146–148] than that with later-onset CRC. BMI has also been associated more strongly with colon cancer than with rectal cancer[157]; however, the rise of early-onset rectal cancer in the USA has outpaced that of early-onset colon cancer[158,159]. Therefore, further studies are needed to clarify the effects of BMI during childhood, adolescence and young adulthood on early-onset versus later-onset CRC risk by tumour location.

Sedentary lifestyle and physical inactivity probably both have a role in early-onset CRC[160–162]. An analysis using the Nurses' Health Study II found that prolonged sedentary television viewing time was associated with an increased incidence of early-onset CRC independent of exercise and BMI[160]. Metabolic syndrome, which encompasses hypertension, hyperglycaemia, abdominal obesity and hyperlipidaemia[151,152,163], as well as individual metabolic comorbid conditions such as type 2 diabetes[148,152,164–167] and hyperlipidaemia[147–149,151,155,165,166], have also been associated with early-onset CRC risk.

Diet-related factors reported to be associated with early-onset CRC risk in certain studies include sweetened beverage intake during adolescence and young adulthood[168], western dietary patterns[169], processed meat intake[170], red meat intake[171], low vitamin D intake[172], limited intake of vegetables, fruits, and micronutrients[170], dietary and lifestyle index linked to hyperinsulinaemia[173] and excessive alcohol consumption[155,164,165,170,171,174,175].

Evidence supporting a role for other risk factors is limited. The use of aspirin and NSAIDs has been associated with a lower risk of early-onset CRC[171,176], whereas inflammatory bowel diseases such as ulcerative colitis and Crohn disease have been associated with an increased risk[147]. Results from studies exploring

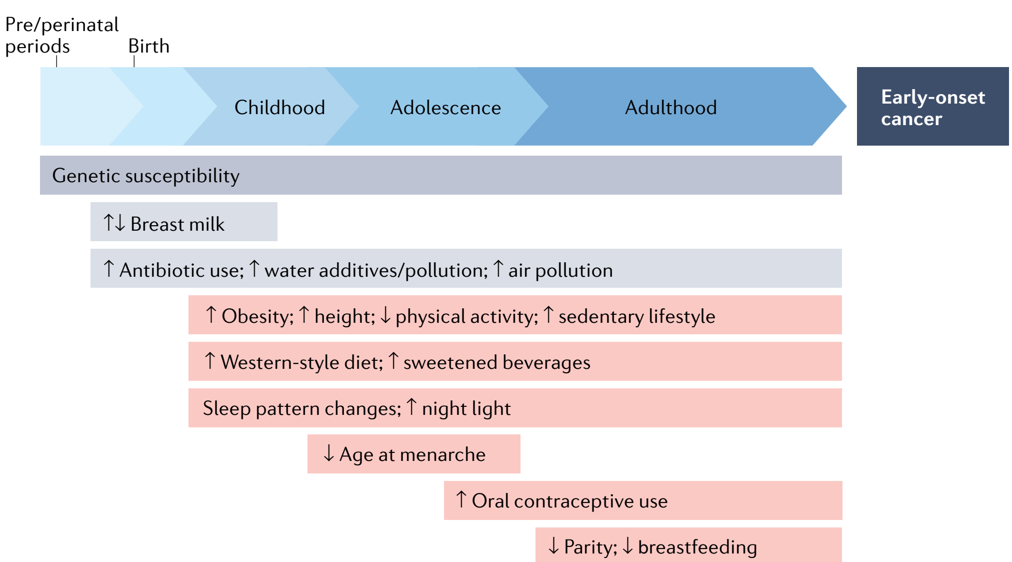

Fig. 2 | **Individual life-course exposures and their relationship with the development of early-onset cancers.** An individual will encounter various exposures throughout life from conception (or even the germ cell period before conception), some of which might also be cancer risk factors. Considering the long latency periods of neoplastic development, risk factor exposures in early life (from conception to adolescence) and during young adulthood are considered to have pathogenic roles in the development of early-onset cancer (defined here as cancer diagnosed in adults ≤50 years of age). Genetic susceptibility results from germline genetic variants with a spectrum from low to high penetrance. Gene–environment interactions can occur at any time throughout the lifetime of an individual. This figure also implies considerable challenges in studying the aetiology of early-onset cancers.

Table 1 | **Possible risk factors for early-onset cancers**

Cancer type	Factors with a generally increasing temporal trend[a]	Factors with a generally stable temporal trend	Factors with a generally decreasing or variable temporal trend*
Breast cancer	Younger age at menarche[106–109], oral contraceptive use[109,110], nulliparity[106,109], older age at first birth[106,109], never-breastfeeding[106], central obesity[115], physical inactivity[124], alcohol consumption[125–128], fat intake[130,131]	Family history of breast cancer[97,136]	Smoking[132–134]
CRC	Obesity[33,146–156], sedentary behaviour[160–162], metabolic syndrome[151,152,163], type 2 diabetes[148,165–167,336], hyperlipidaemia[12,107,109,111,114,115,124], diet (such as western diet, sugar-sweetened beverages, low vitamin D intake and red meat)[168–170,172], alcohol consumption[155,165,170,174,175], inflammatory bowel disease[147]	Family history of CRC[147–149,155,170,177,186–189]	Smoking[149,155,164–166,174,175,177–180]
Endometrial cancer	Obesity[193–195,337]	Family history of any cancer[194,196]	–
Oesophageal adenocarcinoma	Obesity[199], recurrent gastroesophageal reflux[199]	–	Smoking[199]
Head and neck cancer	Alcohol consumption[204], HPV infection in areas without comprehensive vaccination coverage[205,206]	–	Smoking (snuff use)[204,338] HPV infection in areas with comprehensive vaccination coverage[205,206]
Kidney cancer	Obesity[207]	–	–
Liver cancer	–	Family history of liver cancer[218]	Chronic HBV infection[216]
Multiple myeloma	Obesity[223,224]	–	–
Pancreatic cancer	Obesity[225,226], alcohol consumption[227]	–	Smoking[227]
Prostate cancer	–	Family history of prostate cancer[238]	–
Stomach cancer	–	Family history of stomach or prostate cancer[249,251]	*Helicobacter pylori* infection[242]

CRC, colorectal cancer; HBV, hepatitis B virus; HPV, human papillomavirus. [a]Several decades of follow-up monitoring will probably be required to confirm possible effects of early-life exposures on the development of early-onset cancer. Therefore, effects of temporal trends in early-life exposure seen over the past few decades are unlikely to have appeared in the available literature on the incidence of early-onset cancer.

associations between smoking and early-onset CRC have been inconsistent[149,155,164–166,174,175,177–180]. Long-term use of antibiotics has been associated with colorectal adenoma risk in a few studies[181,182], although whether the use of antibiotics is a risk factor for early-onset CRC remains to be determined[183–185].

A family history of CRC has been associated with an increased risk of both early-onset CRC and advanced-stage adenoma[147,148,155,170,186], and the extent of increase in risk associated with a family history of CRC is higher for early-onset than for later-onset disease[147–149,177,186–189]. Most early-onset CRCs are sporadic, although those with a family history of the disease constitute a heterogeneous group with or without hereditary cancer syndromes, such as Lynch syndrome and familial adenomatous polyposis[190]. Studies showed that 16–20%, 5–8% and 5% of patients with early-onset CRC had pathogenic germline variants, Lynch syndrome and polyposis syndromes, respectively[98,99].

Several studies have identified common genetic risk variants for early-onset CRC[94,98,99,191]. A large-scale consortium study demonstrated that a polygenic risk score based on 95 CRC-associated genetic variants is more strongly associated with early-onset than later-onset CRC, particularly in the absence of a family history of CRC and/or Lynch syndrome[94].

Endometrial cancer. Endometrial adenocarcinoma is the most common histological type of uterine corpus cancer[192]. Obesity has been consistently associated with early-onset as well as overall endometrial cancer risk[193–195]. Irregular menstruation and nulliparity are established risk factors for endometrial cancer; however, the role of reproductive factors such as decreasing fertility rates and increasing nulliparity in early-onset endometrial cancer remains to be determined. A family history of any cancer has been associated with early-onset endometrial cancer[194,196], which might in part reflect the link between Lynch syndrome and early-onset cancer. In a cross-sectional analysis, 18% of individuals with early-onset endometrial cancers had presumptive Lynch syndrome[196].

Oesophageal adenocarcinoma. Squamous cell carcinoma and adenocarcinoma are the two main histological subtypes of oesophageal cancer, with differing risk factor profiles[197]. Oesophageal adenocarcinomas tend to be most prevalent in western countries, whereas oesophageal squamous cell carcinomas are more common in certain parts of Asia and a few other geographical locations[198]. According to GLOBOCAN data, the incidence of early-onset oesophageal cancer has increased in a few countries. Notably, an increase in the incidence of early-onset oesophageal adenocarcinoma has been observed in the USA[10].

Possible risk factors for early-onset oesophageal adenocarcinoma include obesity, gastroesophageal reflux disease and smoking[199]. Obesity is (probably causally) associated with gastroesophageal reflux disease[200] and both obesity and gastroesophageal reflux disease have increased in most western countries over the past decades[201,202]. *H. pylori* infection has been inversely associated with gastroesophageal reflux disease[203]; therefore, eradication of *H. pylori* infection might be associated with gastroesophageal reflux disease, which could partly account for the observed trends in the incidence of early-onset oesophageal adenocarcinoma.

Head and neck cancer. Head and neck cancers include squamous cell carcinomas (most common), adenocarcinomas, lymphomas, sarcomas and other rarer subtypes. A pooled analysis of data from 25 case–control studies found associations of smoking, alcohol consumption, a family history of cancer, and lower fruit and vegetable consumption with early-onset head and neck cancer (in the oral cavity, hypopharynx and larynx) diagnosed in patients <45 years of age[204]. Behavioural factors relating to sexual activity, including oral sex (in adolescents), premarital sex and the number of sexual partners have all changed since the mid-20th century in both North America and Europe[205,206]. These changes might have increased the prevalence of oral HPV infection, possibly leading to an increased incidence of early-onset head and neck cancer[205,206]. Whether and how increased uptake of HPV vaccination over the past two decades might reduce the incidence of early-onset cancer remains to be determined.

Kidney cancer. Kidney cancer consists of renal cell carcinomas (RCCs; the most common), urothelial carcinoma of the kidney, and other rarer tumour subtypes. Most published data are based on either kidney cancer overall or RCC specifically[207,208]. Both smoking and physical inactivity have been associated with an increased overall risk of kidney cancer[209–211], although these risk factors have not been evaluated specifically in relation to early-onset cancers. In a registry study including 1.1 million adolescent males, a BMI during adolescence of ≥27.5 kg/m^2 (relative to <22.5 kg/m^2) was associated with a higher incidence of RCC (at a mean of 44 years of age at diagnosis)[207]. Having a first-degree relative (especially sibling proband) with RCC is also associated with a higher risk of early-onset RCC[208].

Liver cancer. Primary liver cancer mostly consists of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma[212,213]. Most published data are based on either liver cancer overall or HCC. Established risk factors for HCC include chronic infection with HBV and hepatitis C virus, chronic hepatitis, cirrhosis, alcohol consumption, obesity, type 2 diabetes, non-alcoholic fatty liver disease and smoking[212]. However, limited data exist on risk factors for early-onset HCC. Data from several studies indicate a lower prevalence of underlying cirrhosis in patients with early-onset HCCs than in patients with later-onset forms of this cancer[214], suggesting the existence of differences in aetiology.

Chronic HBV infection is associated with early-onset HCC[215,216]. Data from a case–control study involving HBV carriers indicate that smoking is associated with early-onset, but not later-onset HCC[217]. A family history of HCC has been associated with an increased risk of an HCC diagnosis at <45 years of age, and the increase in risk is greater in HBV carriers than in HBV non-carriers[218]. Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, which are associated with obesity, might also have contributed to the rise of early-onset HCC[219,220]. The implications of the declining global prevalence of chronic HBV infection, along with changes in smoking and alcohol consumption over the past few decades[64,219], for the incidence of HCC in different age groups remains to be determined.

Multiple myeloma. Both the incidence and mean age at diagnosis of MM vary greatly across ethnicities, regions and countries[221], although an increased incidence of early-onset MM has been reported in several countries[3,8]. This increase at least partly reflects increased uptake of screening for monoclonal gammopathy, although a genuine increase in incidence might also be emerging.

Established risk factors for MM include male sex, Black ethnicity, obesity and a family history of MM[222]. However, data on risk factors for early-onset MM remain scarce. Compared with BMI later in adulthood, BMI at a younger age (25–30 years of age[223], or 18–30 years of age[224]) is more strongly associated with MM risk. Stratified analyses by age at diagnosis were not conducted in these studies[223,224], but the studies still suggest that the trend towards increasing obesity in younger people might contribute to the increasing incidence of early-onset MM.

Pancreatic cancer. Obesity[225,226], smoking[227] and alcohol consumption[227] (all established risk factors for pancreatic cancer) have also been associated with early-onset pancreatic cancer risk. The trends of increasing obesity and alcohol consumption since the early 20th century might have contributed to this rise. Obesity has been associated with a younger age at diagnosis among patients with pancreatic cancer[226]. In a pooled analysis of data from case–control studies, alcohol consumption was more strongly associated with a pancreatic cancer diagnosis at <45 years of age than a diagnosis at ≥45 years[227]. Studies have also shown that 0–8% and 3% of patients diagnosed with early-onset pancreatic cancers have a family history of the disease in any first-degree relative and Lynch syndrome, respectively[228,229].

Prostate cancer. Determining the true trends in prostate cancer incidence independent of the effects of screening based on serum kallikrein related peptidase 3 (KLK3; also known as prostate-specific antigen (PSA)) is typically problematic. Routine serum KLK3 (PSA)-based screening has been less common in men <50 years of age[230]; nonetheless, enhanced uptake of serum KLK3 (PSA) tests is likely to have contributed to an increase in the diagnosis of early-onset prostate cancer. However, a true increase in incidence also cannot be ruled out.

Established or possible risk factors for prostate cancer include Black ethnicity, tall height, obesity, early age at puberty, and high serum levels of testosterone and insulin-like growth factor 1 (IGF1)[231–234]. Evidence also suggests an aetiological role of genetic factors in early-onset prostate cancer[235]. Data from the Nordic Twin Study suggest that the heritability (defined as the proportion of variance for a measure that is attributable to genetic differences in the study population) of prostate cancer risk is high (58%, 95% CI 52–63%)[236]. Data from another study suggest that 43% of prostate cancers diagnosed at <55 years of age arise from the presence of high-penetrance variants[237]. The number of first-degree relatives with prostate cancer is also associated with early-onset prostate cancer risk[238].

Data from a registry-based study from Sweden[239] demonstrate an association between prostate cancer diagnosed at <55 years of age and the use of assisted reproduction techniques, which often reflect hampered spermatogenesis. How factors relating to the inability to reproduce naturally, undergoing enhanced medical work-up or both have contributed to this association remains unclear.

Stomach cancer. Stomach (gastric) cancer, which mostly consists of adenocarcinomas and, less commonly, gastrointestinal stromal tumours, is anatomically classified into tumours of the cardia and non-cardia (fundus and antrum), with differing clinical and epidemiological features[240]. Gastric non-cardia cancer is common in Eastern and Central Asia and Eastern Europe and is associated with *H. pylori* infection[13,240,241]. Gastric cardia cancer is common in North America and Western Europe, and has been associated with obesity[241]. Over the past several decades, the incidence of early-onset stomach (gastric) cancer has increased in some countries, although whether this reflects an increase in either early-onset cardia or non-cardia cancer, or both, remains unclear.

H. pylori infection has been associated with a stomach cancer diagnosis at <40 years of age[242]. The prevalence of *H. pylori* infection has declined in the USA, most European countries, China and Japan[243,244], although it remains relatively high in developing and newly industrialized countries compared to economically developed countries[243,245].

Data from several studies from the USA indicate an association between heavy alcohol consumption and both early-onset and later-onset stomach cancer[246,247]. In a case-only study, BMI correlated inversely with age at stomach cancer diagnosis[226]. Data from several studies demonstrate an association between a family history of stomach or prostate cancer and early-onset stomach cancer[248–251]. An inherited cancer predisposition, such as hereditary diffuse gastric cancer (potentially owing to germline *CDH1* mutations[252]) and Lynch syndrome, increases the risk of early-onset stomach cancer[253–255]. Multiple lifestyle-related factors, including alcohol consumption and obesity, and their interactions with genetic factors, might also have a role in the rise of early-onset stomach cancer.

Thyroid cancer. The increased incidence of thyroid cancer since the 1980s is probably attributable to increased use of diagnostic imaging techniques (such as ultrasonography, CT and MRI) and follow-up fine-needle aspiration biopsy sampling[256–260], which might have led to the detection of many clinically insignificant thyroid tumours. Notably, in South Korea a thyroid cancer screening programme introduced in 1999 led to a substantial increase in the incidence of thyroid cancer shortly thereafter. Most papillary thyroid carcinomas (the most common thyroid cancer subtype) clinically behave as essentially benign tumours. However, because distinguishing between such benign tumours and truly malignant tumours is often impossible, all tumours with certain characteristic nuclear features are diagnosed as papillary thyroid carcinomas. Whether a true increase in the incidence of early-onset thyroid cancer incidence and related mortality exists remains to be determined.

Differences in aetiology and pathogenesis

Accumulating evidence indicates the existence of differences in both clinical and tumour characteristics between patients with certain forms of early-onset and later-onset cancer, including breast cancer[261–269], CRC[94,98,99,187,190,270–282], endometrial cancer[196,283–289], MM[290–294], pancreatic cancer[228,295–298], prostate cancer[299–305] and stomach cancer[246,253,306–309] (TABLE 2). These findings suggest that early-onset and late-onset cancers might have somewhat different mechanisms of carcinogenesis. Tumour tissue analyses of molecular pathology, genomics, multiomics and/or immunological features can provide insights into pathology and explain the links between exposures and specific molecular signatures[310]. Hence, the integration of tumour tissue analyses into epidemiological studies, so-called molecular pathological epidemiology (MPE) research[310], should be considered when feasible.

A major benefit of MPE resides in providing better definitions of tumour phenotype, thus improving our understanding of aetiologies related to host susceptibility and exposures. With the presence of a phenotype-specific association (of a given exposure), the MPE approach can reveal either a moderate or a strong effect size of a specific association, thereby helping to establish causality[311,312]. MPE can have a role in early-onset cancer research by linking unidentified or suspected risk factors (such as certain early-life exposures) to specific tumour phenotypes. Molecular pathological characteristics often by themselves imply specific aetiological underpinnings. For example, the detection of smoking, UV radiation and alkylating somatic mutational signatures suggests exposure to smoke, sunlight and red meat carcinogens, respectively[313,314]. Establishing new exposure–phenotype links will inform our effort to develop strategies for the prevention of early-onset cancer.

Public health and societal implications

Several key steps need to be considered when attempting to address the current issues associated with early-onset cancer (FIG. 3). Given the increasing incidence of several early-onset cancer types, we need to increase the awareness of this trend and potentially re-evaluate current screening guidelines and/or develop personalized screening approaches for early-onset cancer, although further research is needed in this area.

Current evidence suggests that certain early-onset cancer types are more likely to be of an advanced stage and to have worse survival outcomes than their later-onset counterparts (TABLE 2). Therefore, research into therapeutics for early-onset cancers, in addition to primary prevention and early detection, is warranted. Researchers should aim to improve personalized therapeutic strategies. For example, given the established role of microsatellite instability (MSI) status in predicting a response to immune checkpoint inhibitors, testing for MSI or mismatch repair protein expression is indicated in patients with solid tumours, including those with early-onset solid tumours, for personalized treatment planning[315].

Given the global changes in risk factor exposures over the past decades, a possibility emerges that, among all current birth cohorts, younger cohorts (current children, adolescents and young adults) might have higher age-specific risks of cancer throughout life compared to current older people (>50 years of age). The current generation of young adults already have a higher risk of early-onset cancer than older generations. Many cancer risk factors are also risk factors for other chronic diseases, and the incidence and prevalence of other chronic diseases, such as diabetes and inflammatory bowel disease, among children, adolescents and young adults, have increased in multiple countries over the past several decades[45,46,316]. Therefore, this early-onset cancer epidemic could be just one manifestation (the tip of the iceberg) or an example of an increasing trend towards greater incidences of many chronic diseases in young and/or future generations.

Cancer-related lifestyle factors in adulthood often originate from childhood and/or adolescence. Therefore, popularizing a healthy diet and lifestyle (while avoiding unhealthy foods and beverages, a sedentary lifestyle and avoiding the development of an early interest in alcohol consumption and/or smoking) among children, possibly through school meal programmes and educational interventions, is an important method of primary cancer prevention[317]. Avoidance of unhealthy behaviours can benefit both children and parents, enhance their well-being and reduce the societal burdens associated with many chronic diseases and/or conditions.

Reforming the food production and distribution system is also necessary to encourage people to eat healthier foods and fewer (ultra)processed foods and beverages. Policies implementing taxation on sugar-sweetened beverages could lead to reduced consumption and energy intake[318]. Health-related taxes are recommended by the WHO[319] and have been successfully implemented in several countries[320].

In addition, considering the substantial environmental changes that have occurred since the mid-20th

Table 2 | **Clinical and tumour-specific characteristics of early-onset versus later-onset cancers**

Cancer type	Clinical characteristics	Tumour characteristics
Breast cancer	Advanced disease stages at diagnosis, inferior OS[261,263,265,339–342]	Adverse pathological features, including high tumour grade, triple-negative (ESR1 (also known as ER)-negative, PGR (also known as PR)-negative, ERBB2 (also known as HER2)-negative) subtype, ERBB2 (HER-2)-positive subtype, and MKI67 (Ki-67) overexpression[261–269]
CRC	Predilection for rectal and distal localization within the colon, advanced disease stages at diagnosis, inferior OS[94,187,270,271,276,280,343–358]	Aggressive tumour phenotypes (excluding MSI-high status) such as poor differentiation, lymphovascular and perineural invasion, signet ring cell histology, LINE-1 hypomethylation, and lower lymphocytic immune reaction[190,273–282]
Endometrial cancer	Inconsistent findings on OS and disease stages at diagnosis[196,283–289]	Certain studies suggest that early-onset endometrial cancer is associated with favourable features, such as well-differentiated carcinoma and adenoacanthoma[283–287], whereas others suggest that early-onset endometrial cancer is associated with unfavourable pathological features, including poor differentiation, high mitotic rates, and deep myometrial invasion[196,288,289]
Multiple myeloma	–	Certain studies suggest that younger patients have greater numbers of lytic lesions and high-risk cytogenetic abnormalities[290,291], whereas other studies suggest that younger patients have similar or more-favourable tumour characteristics[291,293,294]
Pancreatic cancer	Advanced disease stages at diagnosis[297,298]	Poor differentiation, perineural invasion[228,295–298]
Prostate cancer	Metastatic disease, resistance to androgen-deprivation therapy, and shorter OS[299–302]	Genomic and epigenomic aberrations seen in patients with early-onset prostate cancer might be distinctly different from those seen in patients with later-onset disease[303,304]; for example, clinically advanced early-onset prostate cancers might be associated with *TMPRSS2::ERG* fusions and fewer *AR*, *SPOP* and *ASXL1* alterations[305]
Stomach cancer	More common in women, advanced disease stages at diagnosis[299–302]	Higher grades, advanced disease stages, signet ring cell or diffuse histology[246,253,306]; fewer somatic mutations in *TP53* and more somatic mutations in *MUC5B*, *BANP*, *CDH1* and *TGFBR1* (REFS. [307,308])

CRC, colorectal cancer; LINE-1, long interspersed nucleotide element-1; MSI, microsatellite instability; OS, overall survival.

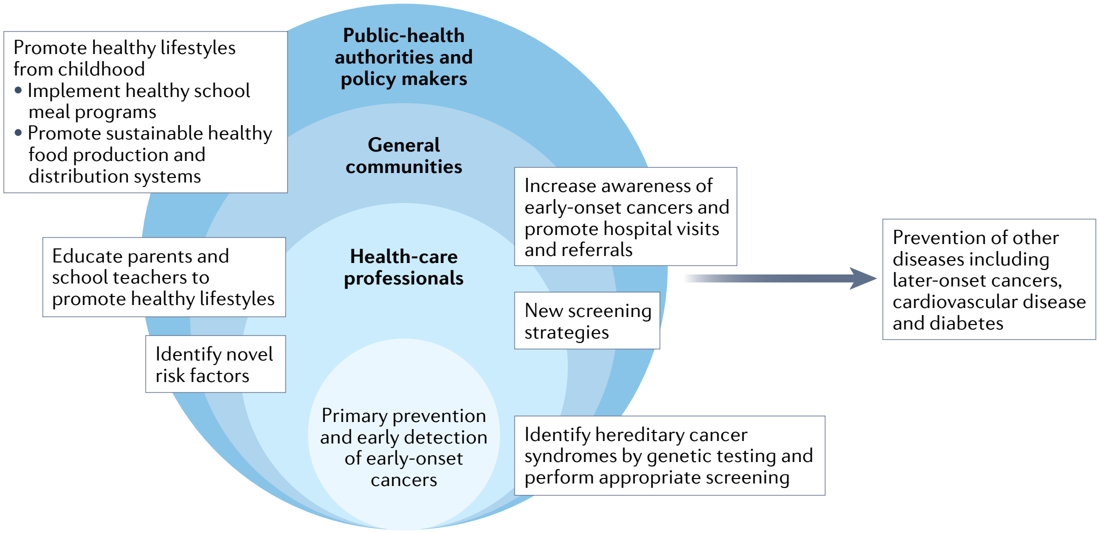

Fig. 3 | **Broad implications and benefits of prevention efforts for early-onset cancers.** Collaborative interventions at multiple levels (such as those delivered by health-care professionals, general communities, public health authorities and policy makers) promoting the early identification of hereditary cancer syndromes, healthy diet and lifestyle behaviours, behavioural education of children and increasing cancer awareness will lead to not only prevention of early-onset cancers (defined here as cancer diagnosed in adults ≤50 years of age) and many other diseases including later-onset cancers (defined as cancers diagnosed at >50 years of age), but also ultimately more sustainable health-care practices.

century, an improved understanding of the effects of exposures in the lived environment (such as air and water pollution) is also crucial. Other less-studied factors that affected several generations during the 20th century include changes in sleep patterns and night-time light exposure. Evidence indicates an epidemiological and pathobiological link between sleep patterns (such as night shift work) and systemic metabolic abnormalities such as obesity and type 2 diabetes[321,322], both of which are cancer risk factors. The International Agency for Research on Cancer has classified night shift work as "probably carcinogenic to humans" (group 2A)[72]. These exposures often relate not only to an individual's habits but also the effects of certain societal, political and environmental influences. For example, many individuals undertake regular night shifts and thus increase their exposure to light during night-time owing to societal demands for shift work. On the other hand, a policy that mandates increased payments for those doing night shifts will create financial incentives for employers to reduce the overall amount of night shift work to an essential minimum. Therefore, research on systematic and structural interventions at the societal level is warranted.

Research gaps and future directions

Substantial gaps exist in research on early-onset cancer. Data from many large-scale cross-sectional and case–control studies are available, although the design of such studies limits the ability to accurately assess early-life exposures, typically owing to reliance on personal recollection as the main source of data. Conducting prospective cohort studies involving early-life participants requires both the co-operation of parents and decades of follow-up monitoring. Currently, only very few cohort studies, in which most participants are of white ethnicity, have monitored individuals from early in life up to at least 40–50 years of age[29,323–326].

Certain technological advances might help address this research gap. First, data from sources such as electronic health records (EHRs) and computational analytical advances (such as those involving natural language processing and/or machine learning) provide many opportunities to evaluate the longitudinal relationships between early-life exposures and disease risk. The collection of EHR data will continue to expand worldwide, also integrating information from clinical omics testing[327]. Second, geospatial data from early-life residence could be used to assess the effects of early-life environmental exposures[328,329]. Third, with rapid advances in biomedical sciences, including in omics analyses, we can assess the molecular profiles of early-onset cancers and compare them with later-onset cancers, which has the potential to provide information on differences in aetiology and guide effective personalized treatment strategies. Furthermore, early-life biospecimens can provide reliable sources for objective biomarker measurements that reflect early-life biological information. Prospective cohort studies combined with early-life specimen collection (including blood, stool, saliva, urine, placenta, umbilical cord and others) would enable early-life factors to be studied in relation to various future health outcomes, including cancer.

Analyses of tumour tissue samples and other specimens can provide valuable pathological and biological insights, although the necessity to collect such specimens from sizable populations while minimizing selection bias remains a substantial issue. Close interdisciplinary collaborations involving investigators with divergent expertise in biomedical and population sciences are essential in addressing this challenge and opening up new opportunities.

Generally, research proposals that appear to promise more-foreseeable, shorter-term results have higher probabilities of receiving funding[330]. To conduct prospective life-course cohort studies furnished with adequate specimen repositories would require a long-term commitment from one or more major funding bodies. In the meantime, existing datasets of populations that include patients with early-onset cancers could be utilized to provide research opportunities. If each dataset is small, pooling of datasets might be necessary to enable robust statistical analyses.

Research on disparities in cancer-related health between sexes and/or between ethnic, demographic and socioeconomic groups currently lags behind the progress made in other areas of cancer research, such as genomics and therapeutics[331]. For example, in the USA, trends in the incidence of early-onset CRC and pancreatic cancer differ substantially by race/ethnicity[332,333]. Many early-life exposures have a varying prevalence in these different societal groups. However, sufficient data on whether exposures differentially affect the risk of early-onset cancers according to sex, race/ethnicity or socioeconomic groups are currently unavailable. Therefore, addressing health disparities requires assessments of geospatial exposure and multilevel approaches encompassing social, epidemiological and pathobiological sciences[334]. Furthermore, the integration of divergent research fields will contribute to a better understanding of early-onset cancers, ultimately leading to improved prevention and treatment strategies.

Conclusions

The incidence of many types of early-onset cancer (those diagnosed at ≤50 years of age) has increased in many countries. The reasons for this phenomenon are not entirely clear but are probably related to changes in risk factor exposures in early life and/or young adulthood from the mid-20th century onwards. The increased consumption of highly processed or westernized foods together with changes in lifestyles, the environment, morbidities and other factors might all have contributed to such changes in exposures. Therefore, although available data on the incidence of early-onset cancers in low-income and middle-income countries are currently limited, the rise of early-onset cancers is likely to be increasingly prominent in those countries, potentially leading to a global early-onset cancer pandemic.

To study the aetiology of early-onset cancers, prospective life-course cohort studies that enable biomarker/omics analyses of specimens obtained during early life are needed. In addition, advances in information technologies combined with artificial intelligence should be leveraged to fill research gaps. We must raise awareness, among both the public and health-care professionals, of the rising incidence of early-onset cancer and aim to increase primary, secondary and tertiary prevention efforts. A reasonable assumption exists that improving heath literacy and interventions that promote a healthy lifestyle, including a healthy diet, could reduce cancer risk. Beyond personal prevention efforts, systematic interventions that promote screening uptake and a healthier lifestyle at the societal level (such as, among others, regulation of industries that produce tobacco, ultraprocessed foods and beverages) could potentially have an effect on cancer risk. We call for collaborations of researchers, health-care providers, public health practitioners, policymakers and the public to address the rising incidence of early-onset cancer.

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