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Review

Early-onset cancers: Biological bases and clinical implications

Gianluca Mauri,[1,2,3,8] Giorgio Patelli,[1,2,3,8] Andrea Sartore-Bianchi,[2,3] Sergio Abrignani,[4,5] Beatrice Bodega,[4,6] Silvia Marsoni,[1] Vincenzo Costanzo,[1,2] Angela Bachi,[1] Salvatore Siena,[2,3] and Alberto Bardelli[1,7,*]

[1]IFOM ETS – The AIRC Institute of Molecular Oncology, Milan, Italy
[2]Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy
[3]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy
[4]INGM, Istituto Nazionale Genetica Molecolare "Romeo ed Enrica Invernizzi", Milan, Italy
[5]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
[6]Department of Biosciences, University of Milan, Milan, Italy
[7]Department of Oncology, Molecular Biotechnology Center, University of Torino, Torino, Italy
[8]These authors contributed equally
*Correspondence: alberto.bardelli@unito.it
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SUMMARY

Since the nineties, the incidence of sporadic early-onset (EO) cancers has been rising worldwide. The underlying reasons are still unknown. However, identifying them is vital for advancing both prevention and intervention. Here, we exploit available knowledge derived from clinical observations to formulate testable hypotheses aimed at defining the causal factors of this epidemic and discuss how to experimentally test them. We explore the potential impact of exposome changes from the millennials to contemporary young generations, considering both environmental exposures and enhanced susceptibilities to EO-cancer development. We emphasize how establishing the time required for an EO cancer to develop is relevant to defining future screening strategies. Finally, we discuss the importance of integrating multi-dimensional data from international collaborations to generate comprehensive knowledge and translate these findings back into clinical practice.

INTRODUCTION

Over the last three decades, cancer epidemiology has been changing remarkably due to the rising incidence of sporadic early-onset (EO) cancers. Traditionally observed in adults over the age of 65, these primarily solid tumors are now increasingly diagnosed in younger individuals under the age of 50[1,2]. Accordingly, the term EO cancers today identifies those solid tumors usually occurring in people aged 60 to 70 diagnosed in individuals younger than 50. However, this definition is merely arbitrary, based on practicality rather than on a biological rationale. EO-cancer incidence is increasing particularly among adolescent and young adults aged 15 to 39.[3–6] This epidemiological shift was initially reported in the USA over the eighties and then confirmed worldwide since the early nineties, progressively emerging as a major public health concern given its physical, social, economic, and psychological consequences.[7–10] Thus, understanding why this is happening, while also defining how to treat young adults diagnosed with cancers, is a priority for oncological research.

Here, we formulate testable hypotheses and suggest a translational comprehensive approach to tackle this epidemic. Starting from reviewing potential causes of EO-cancer increase, we propose how to test several hypotheses through translational platforms, integrating data from both cell-autonomous and non-cell-autonomous models into a comprehensive EO-cancer multi-omics-based assessment (the EO-cancer *integrome*). Understanding the EO-cancer biology, the underlying causes, and the clinical peculiarities of affected individuals is central to identifying preventive and early-diagnosis strategies as well as tailored therapeutic opportunities (Figure 1).

FROM CLINICAL OBSERVATION TO TESTABLE HYPOTHESES

The clinical relevance of EO-cancer rise is highlighted by their emergence as the primary cause of mortality in adolescents and young adults (15–49 years) in world regions with a middle-to-high socio-demographic index, overtaking cardiovascular diseases that predominated in the 1990s.[11] Worldwide incidence of EO cancer increased by almost 80% from 1990 to 2019, and the number of EO-cancer deaths increased as well by around 30%.[12] Indeed, even if with different trends likely due to local environment, lifestyle, and level of available medical treatments, this phenomenon is affecting the entire globe, not being limited to Europe and North America but also affecting Middle East, Australia, and Africa.[12] Projections for the next 15 years suggest that the most common cancers in adults aged 20 to 49 years will be breast (annual increase +0.91%), gastrointestinal, and in particular colorectal (+1.72%), and kidney cancers (+2.16%).[4,7,13] Notably, several other EO-tumor types are also

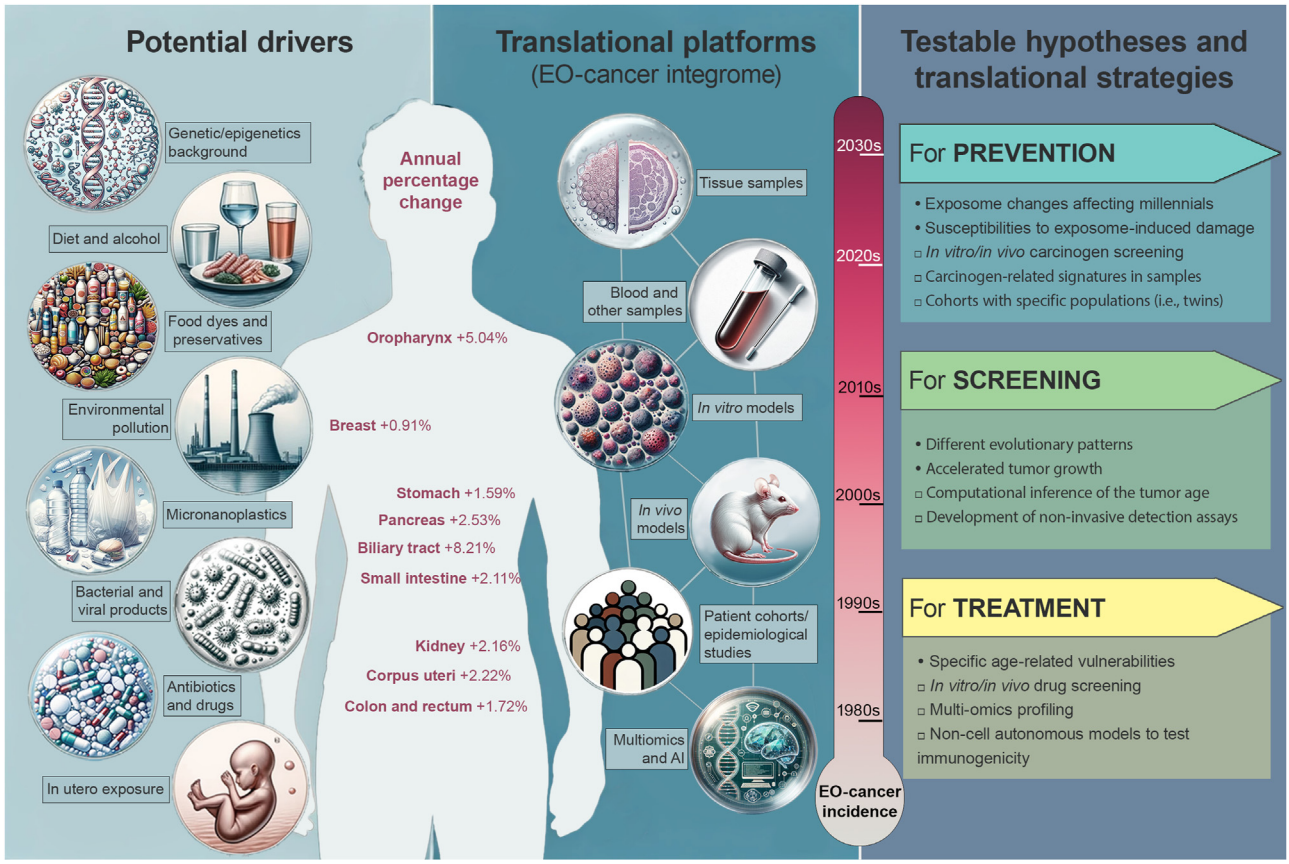

Figure 1. Schematic representation of putative factors contributing to the increase in early-onset cancers (left) alongside with translational platforms (middle) for hypothesis validation (right) within the framework of the "*EO-cancer integrome*"

Keys: •, *testable hypotheses*; ▯, *translational strategies to address hypotheses*; EO, early-onset.

increasing, some with even faster rates including appendix (+15.61%) and biliary tract (+8.12%) cancers.[2,4,7,13] It has been already disproved that enhanced diagnostic workups and screening campaigns are the solely responsible for the increase of EO-cancer diagnoses.[13,14] Breast, digestive, and respiratory EO cancers are particularly lethal in the young adults population.[12] Among all, EO colorectal cancer (EO-CRC) is the most paradigmatic example of this phenomenon, with incidence and mortality both increasing particularly among individuals younger than age 40.[15–18] As a consequence, EO-CRC has recently become the first cause of cancer-related death among males aged 20–49 years in the USA, and current estimates indicate that by 2030 one-third of all CRC will be diagnosed in individuals younger than 50[16,19]. Conversely, mortality for EO breast cancer (EO-BC) and most other cancers is decreasing despite the upsurge in incidence.[7] This disparity is likely due to variations at multiple levels spanning from screening availability to intrinsic biological disease aggressiveness.

An extensive clinicopathological dissection of EO cancers is beyond the scope of our perspective, since it has been already widely addressed elsewhere.[1,20–24] Briefly, EO cancers may present with peculiar clinicopathological features, such as left sidedness in EO-CRC (particularly driven by rectal cancer diagnoses, although with regional differences from Europe to North America),[16–18,25] signet ring features in EO-CRC and gastric cancers, or aggressive non-luminal subtypes in EO-BC.[25,26] Nonetheless, neither significant genomic nor transcriptional differences have been conclusively identified to date, beyond a higher prevalence of gene alterations driving hereditary cancer syndromes.[25,26] As already discussed in previous reviews on this topic, the only genetic and transcriptomic differences between EO-CRC and its older counterpart were a higher prevalence of microsatellite instability and consensus molecular subtype (CMS) 1 features, and a lower prevalence of *BRAF* mutations, likely related to the higher prevalence of Lynch syndrome-related CRC among patients younger than age 50.[15,25–27] Several retrospective studies involving large cohorts of EO-CRC patients did not find any significant differences in the prevalence of both actionable or trunk mutations such as *RAS*, *APC*, and *TP53*.[15,25–28] In addition, despite usually undergoing more intensive medical and surgical procedures in both the adjuvant and metastatic settings, EO-cancer patients do not generally achieve significant survival benefits while potentially suffering from more treatment-related adverse events.[15,29–31] Finally, while anticipating screening initiation for those diseases in which this is feasible has been suggested,

this strategy still represents an empirical biology-agnostic approach and would be in any case limited to specific cancer types (EO-CRC, BC, and cervical cancer).[32] In this regard, even in cancer types where screening anticipation might be theoretically feasible, the socio-economical sustainability of such measures remains questionable.[33,34]

The identification of the biological features of EO cancer is central to determine effective prevention measures and treatment options for this disease. The surge in EO-cancer cases has prompted investigation into the root mechanisms of EO-cancer rise, mostly focusing on the "exposome." Notably, environmental factors, including but not limited to diet and sedentary lifestyles, have changed worldwide in the last century, albeit with substantial geographical variations.[1,35] The interaction of multiple factors, rather than a single causative agent, should be taken into consideration when investigating etiological drivers of EO cancers. Given the intricacies involved in pinpointing causations within this context, efforts to unravel these complexities require a methodological downscaling approach. We list below evidence and related testable hypotheses with respect to the unexpected rise of EO cancers, and specifically EO-CRC, worldwide.

First, which environmental substances, to which millennials and subsequent generations (i.e., Gen Z) were exposed, have changed in the last five decades or so, potentially escalating the EO-cancer incidence observed since the 1990s? Are there defined new epigenetic or immune system susceptibilities in young individuals as they progressed toward adulthood? Second, given that EO cancers have been identified in individuals as young as 20 years, it becomes imperative to question how to understand their pathogenesis. Does EO-CRC diverge from the broadly accepted path of colorectal tumorigenesis, such as the adenoma-carcinoma cascade described by Fearon and Vogelstein[36,37]? Indeed, it is hard to imagine (but possible) that a colonic tumor in a healthy 20-year-old individual has been progressing since early childhood. This observation leads to a critical hypothesis: do these tumors evolve through the same path but more rapidly than in older individuals on account of an already "primed toward tumor development" healthy tissue? Or do they follow a distinctive and biologically different evolutionary pattern? Addressing these questions will have profound implications particularly for secondary prevention strategies. Third, if these tumors or their microenvironment are different, could EO-cancer response and resistance to already available anti-cancer agents be different from cancers affecting older patients? Even more importantly, in the absence of a comprehensive biological dissection of EO cancers, new and potentially specific therapeutic vulnerabilities might be missed. Answering these questions on EO cancers would enable more effective and personalized treatment options from prevention to late-stage disease management. Indeed, relying on treatment algorithms derived from clinical studies that included only a limited number of EO-cancer individuals could lead to a "one size fits all" approach, which may not be suited for this peculiar subset of patients. As an example, pre-menopausal women diagnosed with hormone-positive BC under the age of 40 are known to have a worse prognosis and they are treated accordingly with more intensive treatments usually including cytotoxic regimens.[38] Similarly, even if the prognosis of CRC in younger patients is still debated, clinicians tend to treat them more intensively according to an age-related bias without evidence that this approach actually translates into a survival benefit.[29–31]

THE IMPACT OF EXPOSOME CHANGES FROM MILLENNIALS TO YOUNGER INDIVIDUALS

Most EO-cancer cases used to be attributable to inherited genetic alterations, and the prevalence of these hereditary cases has remained stable over time.[15,39] However, only 20% to 30% of EO-CRC and EO-pancreatic cancers are hereditary, while the remaining are sporadic.[15,39,40] Indeed, the rise in EO cancers is attributed to sporadic cases, whose etiology remains elusive.[20] The underlying causes are then most likely associated with the so called "exposome"[1,35] (Figure 1). Over the last century, due to an unprecedented industrial expansion that led to significant improvements of both welfare and life expectancy, an exponential increase in the number and abundance of substances interacting with animals and humans from their prenatal life onwards has occurred.[24] As a result, the number of potential carcinogens has also increased. Indeed, the carcinogen potential of most commercially available substances is largely unknown, including those routinely involved in food and beverage preparation. Not only mutagenesis but also chronic subclinical metabolic inflammation (*meta-inflammation*) induced by Western lifestyle may have contributed to the anticipation of cancer development in youngsters by promoting its development through the modulation of de-differentiation, proliferation, and immune downregulation.[41,42]

Several putative culprits have emerged so far.[1,20,24] From epidemiological studies, we learnt that diet Westernization has led to a higher exposure to well known carcinogens such as 2-Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP), carcinogenic N-nitroso compounds, and polycyclic aromatic hydrocarbons, which are widespread particularly in fast foods, frozen meals, and cured meats particularly in metropolitan areas.[43,44] Recent studies indeed showed a potentially different prevalence of EO cancers between metropolitan and rural areas, thus unmasking a potential heterogeneous geographical distribution of EO-cancer risk factors.[17,18] These molecules, coupled with a deficit in protective nutrients such as vitamins supporting DNA repair and radical oxygen species detoxification, may have contributed to the rise of EO cancers through the induction of DNA adducts and promotion of oxidative stress.[45,46] Since these compounds would have limited time to induce DNA mutation accumulation in young subjects, their potential carcinogenic effect raises questions about the mechanisms involved. One hypothesis to explore is whether the compounds could directly impact the epigenetic configuration of the EO-cancer cells of origin, leading to an acceleration of neoplastic transformation. In this context, microbiome alterations and dysbiosis could also play a role in the development of gastrointestinal tract tumors and other cancers.[47,48] Moreover, low levels of physical activity, obesity, metabolic syndrome, lower level of specific vitamins such as vitamin D, type 2 diabetes, and less favorable socio-economic conditions that are often associated with a higher consumption of processed and low-quality food have been correlated with a higher risk of developing EO cancers.[33,49–56] Also, a link between diet habits and microbiota

was suggested, related to particular microbial metabolism of dietary sulfur compounds that are gastrointestinal carcinogens.[57] In contrast, data about the role of alcohol and its metabolites as culprits of EO cancers are conflicting since, particularly in high-income countries, a trend toward less alcohol consumption was described among adolescents and young adults.[58–60] Opposite trends were reported on the intake of free sugars and high-fructose corn syrup (HFCS) from sweetened beverages and processed foods, which have been linked to the pathogenesis of various cancer types due to their role in metabolic dysregulation and also direct oncogenic effects.[61–63] For example, a causative role of HFCS on promoting the development of CRC in preclinical models has been demonstrated.[62] Likewise, the use of dyes, preservatives and color additives has gradually spread, particularly in candies and sweetened snacks being consumed by children and adolescents.[64,65] In this regard, initial data are emerging about the potential carcinogenicity of dyes such as Red40, a petrol-made colorant.[66] However, assessing the carcinogenicity of such agents is hampered by their heterogeneity and scatteredness in several types of foods, thus requiring experimental platforms to test hundreds of them (and their combinations) on selected preclinical models. Overall, scant studies, mostly case-control and only a few prospective, epidemiologically investigated the impact of dietary risk factors in EO cancers. To improve this knowledge, the DEMETRA international study (NCT05732623) is currently ongoing aiming to compare the associations of specific dietary and lifestyle factors in EO-CRC patients compared with healthy age- and sex-matched controls in countries with increasing versus stable or decreasing EO-CRC incidence, adopting a semi-quantitative food-frequency questionnaire. Finally, the extensive use of fertilizers, pesticides, antibiotics, and hormones in both agriculture and livestock, ultimately contaminating both vegetables and meat, could also be linked to the rise of EO cancer.[67,68]

Notably, changes of the exposome are not limited to diet and exercise habits. The indiscriminate use of common medications such as antibiotics could also be linked to EO cancers for at least two reasons: their impact on gut microbiota and the genotoxicity of some of them on human cells.[69–71] Moreover, excessive and/or improper prescriptions of antibiotics also in newborns, children and adolescents have exponentially increased the overall exposure of individuals to these drugs since their youngest age.[72] Similarly, other medications emerged as potentially associated to EO-CRC, such as beta blockers and *Valeriana officinalis*.[73] Paralleling pharmacological concerns, the exposure to specific bacteria or viruses could have a carcinogenic impact on human cells.[74–76] Interestingly, the role of colibactin, a bacteria-related genotoxin, is under investigation as a potential cause of EO-CRC[77,78] and for its impact on response to treatment of CRC cells to standard chemotherapeutic agents.[79]

Air pollution by means of PM2.5 was recently shown to drive the development of *EGFR* mutant non-small cell lung cancer (NSCLC) by inducing oxidative stress and downregulating immune system surveillance on preexisting *EGFR* mutant non-tumoral lung cells.[80] Considering that most of sporadic NSCLCs in young adults are oncogene addicted (mostly through rearranged *RET*, *ALK*, or *ROS1* genes), whether PM2.5 might also foster cancer development in younger individuals harboring initiating events such as oncogenic translocations in their lung epithelium should be investigated further.[81,82] Moreover, such tumor promoter effects could not be limited to NSCLC and also extend beyond air pollution.[83] Indeed, the ubiquitous contamination of the environment by plastic micro- and nanofibers is another emerging threat for public health.[84,85] It has been suggested that micro- and nano-plastics can accumulate in different organs, leading to neuroendocrine disfunction, cardiovascular events, inflammation and cancers.[86–88] These particles can act as vectors for other carcinogens but also induce inflammation, while plastic-driven cell autonomous impact is yet to be proven.[89] Indeed, *in vitro* and *in vivo* studies only report the effect of acute exposure to micro and nano-plastics on cell lines that are already cancerous, thus limiting the draw of definitive conclusions.[84,90] Formal demonstrations upon *in vivo* and *in vitro* chronic exposure on both cell-autonomous and non-cell autonomous models are warranted. Additionally, micro and nano-plastics are obtained through manipulation with chemical compounds, such as bisphenol A, which could also have cancer initiating and/or promoting action.[91,92]

All above mentioned exposure hypotheses could impact embryonic development *in utero.*[93–95] Related to this, knowledge about the ability of environmental and dietary substances to bypass the blood-placental barrier is critically lacking.[24] Investigating maternal exposures to the aforementioned substances would also be important. Interestingly, the incidence of EO-CRC began to rise in the early 1990s, decades after the increase in later-onset CRC. This time lag suggests the presence of a so-called "birth cohort effect" (i.e., the unique exposure of a group as they move across time), further underscoring the importance of early-life risk factors for the observed increase in the incidence of EO cancers. For instance, the growing adoption of medical procedures such as Cesarean sections, projected to be performed in nearly one-third of all births by 2030, has been suggested to be related to greater odds of EO-CRC in females compared with individuals born through vaginal delivery, highlighting a potential role of early-life gut dysbiosis in this population.[96] Finally, increased rates of appendicectomies and tonsillectomies over the nineties, as well as the spread of bottle feeding and the increased use of antibiotics in the perinatal days should be also investigated as they could alter the initial constitution of children's microbiota and immune system proficiency.[97–99]

THE SPECTRUM OF ENHANCED SUSCEPTIBILITY TO EO-CANCER DEVELOPMENT

Beyond exposure to carcinogens, another layer of complexity involves the interaction between these compounds and genetic, polygenic, or epigenetic predispositions.[72,100–102] Indeed, while hereditary cancer predisposition syndromes are well-characterized, clinically recognized, and have been epidemiologically stable, the role of polygenic non-Mendelian predispositions, including single nucleotide polymorphisms and epigenetic modifications, is less explored.[103,104] In this context, it is unlikely that epidemiological studies adopted hitherto will provide thorough insights on the complexity of the phenomenon. Most importantly the impact of susceptibility modifiers on the initial transformation of healthy cells into cancerous ones, or in promoting growth and

aggressiveness of existing cancerous cell, or even in immune evasion and inflammation are worthy of investigation.

Proficiency of the immune system is critical in restricting cancer development. Accordingly, its deficiency may accelerate the onset of EO cancers and facilitate their spread. Beyond major immune deficiency syndromes allowing for cancer developments,[105,106] we do not actually know how to measure immune related anti-cancer proficiency in newborns and young adults.[107] Indeed, the complexity of the immune system and its interplay with cancer cells and the exposome is such that we currently lack robust clinical metrics to estimate, at the individual level, the anti-cancer proficiency of the immune system beyond that of peculiar immune depressive syndromes.[35,41,108]

It has been increasingly reported that the millennials and subsequent Gen Z generations are increasingly suffering from mental health issues and emotional distress like burnout syndromes, severe depression and sleep disorders.[109,110] The extent to which these conditions affect the immune anti-cancer proficiency remains unknown. Of note, a recent study reported that emotional distress could lead to poorer response to immune checkpoint inhibitors when treating melanoma in the neoadjuvant setting.[111] This result suggests that individual susceptibility to EO-cancer development, progression, and treatment response could extend well beyond genomic and epigenetic factors, encompassing aspects like mental health and circadian rhythms that were previously underestimated.[112] Systematic investigation of these factors, which could be implicated in driving response to exposome exposure, is therefore warranted to understand EO-cancer biology and rise in young populations.

PECULIAR EVOLUTIONARY AND GROWTH PATTERNS OF EO CANCERS: IMPLICATIONS FOR EARLY DIAGNOSIS

The pathogenesis of EO cancers, particularly EO-CRC, presents a compelling area of translational investigation. According to the Fearon and Vogelstein model, CRC usually develops over a period of 5–10 years following well-defined molecular paths.[36,37,113] This model is supported by clinical evidence and primarily by the efficacy of current colonoscopy-based screening campaigns in reducing CRC incidence in individuals with polyps.[18] It is critical to assess whether the traditional "*Vogelgram*" progression can occur faster, as an example in only one to three years, in individuals younger than 40 where EO-CRC is increasing the most.[15,16] We highlight this possibility since we consider questionable that a colonic tumor could start growing in individuals aged 10–15 in the absence of a germline predisposition. One possibility is therefore that the impact of the current exposome on a still unknown pattern of individual risk factors in early-life stages might induce a massive deregulatory event that can affect chromatin and specific DNA areas such as gene enhancers and promoters, ultimately leading to faster cancer development in adolescent.[114]

The possibility of an accelerated development of EO-CRC raises pragmatic clinical considerations. Indeed, the anticipation of current screening protocols, such as fecal occult blood tests and colonoscopy, can only be effective for early detection if EO-CRC develops according to the "classical" timelines of the Vogelstein model.[32] This is particularly relevant in EO-CRC since, compared to other EO cancers, its mortality is increasing and the most widely applied screening procedures are invasive.[7,19] Accordingly, the development of non-invasive screenings such as blood-based tests that consider the timelines of EO-CRC pathogenesis in younger individuals, accounting for the age of onset, speed of tumor development, and EO-cancer biology might be most relevant.[115] Detection of circulating tumor DNA (ctDNA) and plasma proteomics-based assays might be advantageous in this setting allowing more frequent testing given to limited invasiveness, with the possibility of performing a colonoscopy as a follow-up procedure, in contrast with cancers in other sites (i.e., lung, pancreas) where follow-up investigations after a positive ctDNA test might be more invasive or less definitive.[116,117] In this regard, ctDNA monitoring might be effective for early detection of standard-onset CRC.[118] However, its adoption as a screening procedure is still significantly hampered by several factors, such as unknown clinical utility (no definitive proof of cancer-related mortality, despite increased compliance is suggested), low sensitivity for pre-malignant lesions, high analytical costs with no cost-effectiveness analysis, large blood amounts required (around 60 mL), and finally limited specificity.[118–120]

A DEFINITION OF EO CANCER: SPORADIC SOLID TUMORS ARISING BEFORE THE AGE OF 40?

Establishing an operational definition of EO-cancer age threshold is central. The vast majority of current studies have adopted a prespecified age cut off of less than 50 years based on the entry age of screening recommendations which however lacks a biological rationale. Since EO-cancer incidence is increasing the most among patients under the age of 40, focusing on these patients is more likely to pinpoint the actual biological peculiarities of EO cancers. Doing so could represent a pragmatic winning strategy. Since to date these patients represent roughly one-third of all EO-cancers cases, building international multi-institutional networks will be crucial to get the required number of samples to be experimentally exploited to draw remarkable conclusions. While relying on age 40 as a pragmatic cut-off to identify EO-cancer patients for sampling and translational profiling may be practical, this could still represent a limitation in large cohort studies focusing, as an example, on treatment outcomes among EO-cancer patients. This is since, to date, no prespecified age cut-off relies on a biological rationale. In a clinical research context, whenever statistically applicable in large sample size cohorts, age could be considered as a continuous variable (i.e., in the context of translational biobanks), thus avoiding the bias of a prespecified not-biologically driven cut-off. Indeed, we suggest age cut-offs to be considered instrumental to the purpose of a study rather than a dogma to adhere whenever dealing with the topic of EO cancers.

TOWARD EO-CANCERS CLINICAL MANAGEMENT IMPROVEMENT

Whether EO cancers are biologically distinct entities with divergent evolutionary trajectories as compared to their later-onset counterparts may also have implications for the efficacy of

Table 1. Translational platforms and study design exploitable in the context of early-onset cancers (the "EO-cancers integrome"): Advantages and disadvantages

Type of model	Opportunities	Limitations
Patients' samples		
Tumor FFPE or OCT blocks/slides	• widely available, allowing large cohorts. • routinely collected through standardized medical procedures.	• DNA, RNA, and proteins might have been at least partially altered by fixation processes. • intra- and inter-lesion tumor heterogeneity. • spatial-omics feasible but still expensive and not capturing the whole tumor complexity (single slide).
Tumor and matched normal fresh tissues (not fixed)	• high-quality DNA, RNA, and proteins for multi-omics characterization. • single-cell analysis feasible. • immune cells available for isolation and analysis. • source for preclinical model establishment.	• not routinely collected, small cohorts available. • immediate processing mandatory. • prospective collection only, thus requiring long time to reach a reliable sample size. • germline profiling feasible but potentially hampered by field carcinogenesis in cancer patients.
Tumor and matched normal fresh frozen tissues (snap or vitally)	• high-quality DNA, RNA, and proteins available for multi-omics characterization. • single-cell analysis feasible. • source for preclinical model establishment (if vital). • availability in biobanks.	• not routinely collected, small cohorts available. • germline profiling feasible but potentially hampered by field carcinogenesis in cancer patients. • freezing and thawing processes can affect cell viability and functionality.
Blood samples (plasma and PBMCs)	• immune system cells available for isolation and analysis. • germline profiling feasible. • potential ideal source of biological material in screening for early diagnosis (genomic assessment? microRNA?).	• not routinely collected. • patients' compliance required for repeated sampling. • high volume of blood (up to 60 mL).
Buccal swabs and feces	• microbiota assessment feasible.	• not routinely collected. • patients' compliance to provide samples.
Translational models		
Tumoroids	• drug screenings feasible. • 3D models. • co-culturing with microbiota and immune compartment cells.	• mostly cell-autonomous model. • do not allow the evaluation of drug and carcinogen metabolism.
Organoids from healthy mucosa	• carcinogenesis experiments feasible. • 3D models. • co-culturing with microbiota and immune compartment cells.	• mostly cell-autonomous model. • adjacent mucosa derived is frequently primed by field carcinogenesis in cancer patients. • samples from healthy patients are difficult to obtain and require dedicated protocols for collection. • do not allow the evaluation of drug and carcinogen metabolism.
Cell lines	• easy handling for mechanistic experiments. • drug screenings feasible. • carcinogenesis experiments feasible in adenoma models.	• cell-autonomous model. • 2D models. • do not allow the evaluation of drug and carcinogen metabolism. • normal epithelium is difficult to grow and treat. • adenoma cell lines are primed to become a tumor.

(*Continued on next page*)

Table 1. *Continued*

Type of model	Opportunities	Limitations
Murine models	• non-cell-autonomous model. • carcinogenesis experiments feasible. • patient-derived xenografts feasible. • drug screenings feasible. • interaction between tumor and immune system assessable upon drug or carcinogen exposure. • young mice available to differentiate carcinogenesis and response to treatment compared to older mice. • both genetic and chemically induced carcinogenesis feasible.	• most models already predisposed to develop cancers if comparing results with sporadic EO cancers. • non-human models with genomic and metabolic differences. • differences between human and murine immune systems (human HLA versus mouse MHC in epitope recognition). • different drug and carcinogen metabolism (i.e., PhIP). • strict ethical regulation. • limited lifespan.
Patients' cohorts		
Retrospective cohorts	• easily gathered through archive reports. • time coverage of decades allowing large sample size.	• age cut off usually set at 50 years. • risk of recall biases for carcinogen exposure. • missing data are common. • high level of patient heterogeneity. • tissue samples might not be available, especially fresh frozen.
Prospective cohorts	• prospective exposome monitoring feasible. • monitoring EO-cancer trends over the years, also comparing different countries. • possibility of intervention (i.e., treatment).	• age cut off usually set at 50 years. • patients' compliance. • long time to observe meaningful results (i.e., >10 years). • need for multi-center accrual.
Population studies/epidemiological studies	• large sample size. • change to evaluate association with comorbidities. • already ongoing as projects of national interest in many countries.	• age cut off usually set at 50 years. • missing data are common. • high level of patient heterogeneity. • only exposure data, or at most genomics in plasma. • tissue samples usually not available.
Very specific populations/twins	• unprecedented chance to study individuals sharing the same genome (homozygous) but possibly affected or not by EO cancers. • chance to compare environmental exposure (exposome) on top of genetic predisposition.	• ethical issues to study the cancer-free twin. • available registries might not have translational models available for characterization.

FFPE, formalin-fixed paraffin-embedded; OCT, optimal cutting temperature compound; PBMCs, peripheral blood mononuclear cells; HLA, human leukocyte antigen; MHC, major histocompatibility complex; PhIP, 2-Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine

surgical and medical treatment modalities. Clinicians are prone to overtreating EO-cancer patients with more intensive surgical and medical approaches, despite the fact that this approach lacks evidence of improved survival benefits compared to the older population while exposing young individuals to more side effects impacting their quality of life.[29–31,121–123] We and others have previously hypothesized that a subset of EO cancers may respond differently to therapies that are typically effective in standard-onset cancers, such as cytotoxic chemotherapy and/or immunotherapy.[29,124–126] Not only the presence of specific genetic and epigenetic signatures in EO cancers might make them more resistant to drugs that are otherwise effective in older patients, but also distinct tumor microenvironment and microbiota may influence drug efficacy and resistance mechanisms.[79,127]

Development of tailored treatment strategies will require comprehensive multi-omics profiling of EO cancers to identify (if they exist) molecular features underlying druggable alterations.[128] The assessment of the potential role of colibactin could be instrumental to this end.[79] Moreover, exploration of novel therapeutic regimens might include combinations of both novel or already existing targeted therapies, immunotherapies, and traditional chemotherapies to translationally refine the way we treat EO-cancers patients. Overall, such research efforts should not only aim at improving treatment efficacy but also to minimize adverse effects, thereby enhancing the overall quality of life of younger cancer patients both in the short and later term, particularly for those who will be long-term cancer survivors.[129,130]

THE EO-CANCER *INTEGROME*

Disentangling the effects and interactions of concomitant exposures and underlying predispositions, together with the underlying tumorigenesis and evolutionary trajectories of EO cancers will be challenging. Effective integration of epidemiological and cohort studies, analyses of exposure and clinicopathological data, EO-cancer-dedicated sample biobanks and patient-derived preclinical model platforms will be central to success (Table 1; Figure 1). Indeed, availability of samples and models

from EO cancers remain very limited, thus hampering research pace in this field similarly to what happened in the past with rare malignancies, which greatly benefitted from international networking.[131] Different types of preclinical models should be exploited in the field of EO cancers according to the goal of each specific research question: patient-derived tumoroids or xenograft represent the best models toward identifying specific therapeutic options (Table 1),[132–134] while organoids from healthy mucosa and *in vivo* mice models might be instead those most appropriate toward understanding the potential role of carcinogenesis and promotion.[62] Coculturing models rather than *in vivo* mice models could be exploited to investigate the role of the immune system in EO cancers (Table 1).[135,136] Once analyzed, these biorepositories could yield critical insights into the impact of single and combined variables, driving new biological knowledge and treatment opportunities. In this context, an integrated analysis will be mandatory including anamnestic clinical information, exposome data, high-depth tumor and matched-normal profiling (i.e., genetics, epigenetics, transcriptomics, proteomics), and experimentally generated results on preclinical models. This approach ultimately retains the potential of underpinning interactive effects and providing a more comprehensive understanding of the multifactorial nature of EO-cancer etiology and pathogenesis. This approach is what we believe will eventually lead to the development of the "*EO-cancer integrome*". Initial steps in this direction have already been taken and reported feasible, as already witnessed by recent publications in the field of EO-CRC.[137–139]

Integrating different data sources is key for addressing the EO-cancer challenge, and the increasing availability of artificial-intelligence-based tools will be instrumental toward integrating different omics, with clinical and epidemiological data.[140] This involves different study designs and platforms, each with its unique set of advantages and disadvantages, that are discussed in Table 1.

Preclinical models will also be central to mechanistically and functionally test the hypotheses that we have put forward in the previous paragraphs. Both tumor and healthy epithelial models should be effectively leveraged to perform carcinogenesis experiments and drug screenings[132,141,142] (Table 1). Immunotherapy has unequivocally shown that many tumor types develop and become clinically evident in adults because of immune response suppression by the tumor micro-environment. T lymphocytes isolated from tumor tissue samples and peripheral blood mononuclear cells (PBMCs) collected from EO-cancer patients could be co-cultured *in vitro* with tumoroids derived from tumor tissues so to assess cancer immune-editing phenomena and to determine whether anti-cancer immune responses elicited in EO cancers are different from later-onset tumors,[143,144] and whether there is a signature in intratumoral and peripheral T cells potentially associated with immune response failures specific for EO-tumors. Beyond these coculturing systems, exploiting *in vivo* models, mostly murine, could be central to dissect the effect of potential carcinogens in a system mimicking the exposure in humans[145] (Table 1). However, it is important to acknowledge the *in vivo* limitations due to differences between human and murine immune systems, such as human leukocyte antigen (HLA) versus mouse major histocompatibility complex (MHC) in epitope recognition. Therefore, results from murine studies should be interpreted with caution. To mitigate these limitations, the use of humanized mouse models that better mimic human biology, like transgenic HLA mouse models or by engraftment of human $CD34^+$ hematopoietic stem cells, might be possibly explored.[146]

Finally, advanced computation and data modeling will be pivotal in extracting meaningful insights from the vast volume of experimental wet and *in silico* generated data. For instance, specific signatures associated with carcinogen exposure have been reported for a wide range of putative exposures and could be effectively utilized in this setting.[147]

A LIMITATION STILL UNDER DEBATE: DEFINING THE EXPERIMENTAL READOUT

A limitation to the aforementioned experimental platforms remains the identification of an unequivocable readout. In this regard, the identification of EO-cancer-distinctive biologic, genomic, and transcriptomic features (if they exist) is key to further progress. For example, disruptive events such as long interspersed nuclear element-1 (LINE-1) demethylation or chromothripsis might drive EO-cancer development and their occurrence could be used as a proxy in carcinogenesis experiments.[148,149] As previously discussed, the identification of genomic signatures related to carcinogen exposure might shed further light on DNA damage induced in EO cancers even if carcinogenicity can only be postulated upon exposure.[147] Relevantly, it is currently unknown whether the rise of different types of EO cancers, such as EO-BC and EO-CRC, are driven by the same or different causes. This of course could significantly impact also on the type of shared or different readout to be adopted in the experimental translational setting.

CONCLUSIONS

Identifying the causes of EO cancers is mandatory to protect the next generations from this unprecedented epidemic. In this context we have highlighted how clinical, epidemiological, and experimental translational findings should be integrated to gather comprehensive knowledge of the biology of EO cancers.

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AUTHOR CONTRIBUTIONS

G.M. and G.P. conceived the study, reviewed current literature on the topic, and wrote the manuscript. A. Bardelli conceived, wrote, and critically reviewed the manuscript, providing preclinical and translational background toward hypothesis generation. S.S. and A.S.-B. provided clinical contextualization and critically reviewed the manuscript, mostly from a clinical standpoint. S.A. provided immuno-oncology expertise and critically reviewed the manuscript. B.B., V.C., and A. Bachi provided their expertise in multi-omics applied to cancer and critically reviewed the manuscript. S.M. has strong expertise in master observational trials, translational platforms, and biobanks and edited and critically reviewed the manuscript.

DECLARATION OF INTERESTS

A. Bardelli reports personal fees from Guardant Health and Inivata during the conduct of the study as well as grants from AstraZeneca, Boehringer Ingelheim, and NeoPhore outside the submitted work; in addition, A. Bardelli is a shareholder of NeoPhore and Kither. G.M. and G.P. received honoraria from COR2ED. S.S. is an advisory board member for Agenus, AstraZeneca, Bayer, BMS, CheckmAb, Daiichi Sankyo, Guardant Health, Merck, Novartis, Roche-Genentech, and Seagen. A.S.-B. reports personal fees from Amgen, Bayer, Pierre Fabre, Servier, Guardant Health, and Novartis during the conduct of the study.

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