Early-onset cancer with particular reference to colon-rectal cancer

Cancers in the age range from 14 to 49 years old patients might differ in specific risk factors and genetic background from the same cancer side for persons at the age of 50 years onwards. Early-onset colon rectal cancer (EoCRC) in males and females, besides breast cancer, is one of the drivers for the rising incidence of early-onset cancers (EOC).

Early-onset cancer (EOC) is recognized as an emerging new public health problem (1-3). An international group recently explored the global trend in the incidence and death of EOC, finding an almost 80% increase in incidence and a nearly 28% increase in death from 1990 to 2019 (4). The investigation was based on the database Global Burden of Disease for 29 cancers in 204 countries, according to the International Classification of Disease 9th revision (ICD-9) (5). Those melanomas diagnosed in persons aged 14 to 49 were defined as EOC. The estimated annual percentage change (EAPC), as well as age-standard rate (ASR), age-standard incidence rate (ASIR), and standard death rate (ASDR) were calculated. The disability-adjusted life years (DALYs) and risk factors were also assessed.

The global distribution of EOC

Overall, the EOC incidence affected 3.26 million individuals in 2019. Breast cancer was among the EOC, with the highest incidence increase, with 13.7 per 100.000 in 2019 (95% CI 12.5 to 15). The EOC breast cancer rate amounted to 348.1/100.000, and the EOC for respiratory tract cancers was the highest for men with 1676.6/100.000. Also, nasopharyngeal and prostate cancer annual incidences have risen. The highest burden in death and DAILY in adults below 50 years old were accounted, besides breast, also to cancers of the respiratory tract, the stomach, and colorectal cancers. For Oceania, an increase in death because of breast cancer was found to be 32%, and for South-East Asia, 20% (6).

Those regions mainly affected are high-income countries in North America, Western Europe, Australia, and New Zealand (7). The highest ASIR was found in North America (273.2 per 100.000) and the lowest in Western Sub-Saharan Africa (37.4/100.000). Oceania had the highest ASDR with 39,1/100.000, followed by Eastern Europe and Central Asia. The high-income countries in Asia-Pacific had the lowest ASDR, with 16.3/100.000. Certain regions stand out of the general picture with incident increase rates, such as the United Arab Emirates, Qatar, and Saudi Arabia (4). Several environmental factors are supposed to partly increase the risk of suffering from cancer relatively early in life and probably differ in magnitude among the geographical regions.

Risk factors of EOC

The main risk factors for EOC included alcohol consumption, tobacco use, physical inactivity, and obesity. Nutritional risk factors were also found for EOC, in that high portions of red meat, rarely fruits, and seldom milk, but high salt intake was a remarkable risk pattern (6). While smoking can be assumed to be the leading risk factor for respiratory tract cancers in men, the factors behind Asian women's burden for breast cancer death remain ambiguous. For early-onset

breast cancer, smoking and alcohol consumption seem to play a significant role regardless of menopause, but mainly smoking appears to be related to premenopausal breast cancer (8, 9). Predominantly, the main factors are the same for the older population groups, except for the high fasting plasma glucose (4, 7).

Cancer sides mainly affected

Preceding observations of the increase of EOC for particular cancer sides within the previous three decenniums (4) had been for breast- (10), esophageal- (11), gastric- (12), and pancreatic cancers (13). A population-based study also revealed changes in the incidence of colorectal cancer (CRC) (14). This type of cancer was found together with breast-, lung-, and stomach cancer to be linked to the highest death and DAILY burden on a global basis (7).

Increase of early-onset colorectal cancer (EoCRC) and possible reasons

The incidence of early-onset colorectal cancer (EoCRC) was measured worldwide to more than 225,700 cases in 2019, with a rate of 5.7/100.000. Over 86.500 patients succumbed to the disease, with a death rate of 2.2/100.000. The highest incidence rate was observed for China at 12/100.000, while the lowest incidence rates were recorded between 1.2/100.000 to 1.6/100.000 for sub-Saharan Africa (15).

One of the reasons for an increase in EOC might have been the reaction of the health authorities to promote screening, expanding the eligible age range, especially for cervical cancer and CRC (16, 17). Similar initiatives of the health authorities are not restricted to the USA, and adding younger age groups to the screening attempts might increase the incidence of those cancers overall (18). From the younger age groups, the ones 40 to 49 years old are particularly hit by the increase of EOC (6). The rise in EOC might be much higher, as reported in the middle- and low-income countries, because of incomplete data collection. The risk factor pattern described for high-income countries might also have increased in low- and middle-income countries due to an expansive change in lifestyle and nutritional factors.

Obesity in adolescence and adulthood was a risk factor for EoCRC in a cohort of healthy nurses aged 25 to 42 (Field(19). Also, according to the database of the Nurses' Health Study, physical inactivity, such as sitting and using TV and internet facilities as a primary lifestyle behavior, is a risk for colon rectum cancer at younger ages (20). A case-control study pointed to metabolic syndrome, hypertension, hyperglycemia, and type 2 diabetes mellitus being a risk for EoCRC, as already mentioned for EOC in general (21).

Are EOC and EoCRC different types of malignancies compared to cancers in older age?

It might be that in younger age groups, the clinical occurrence of EOCs does not mirror those in the older age groups but occurs as a particular kind of cancer (7). The clinical picture of CRC in certain aspects differs from the later onset of colorectal cancer. Cancer predilection for EoCRC is on the left side of the colon close to the rectum, while for late-onset CRC, it is more on the right (2). EoCRC often has a family history, and the cancer is detected in a relatively late stage of development with metastases in the lung and the pancreas (22). By comparing early-onset- with

late-onset colorectal cancers within the Arab scene, the authors proposed that EoCRC is a distinct disease different from CRC in older patients (23).

Could EoCRC be a problem for Thailand as well?

EoCRC is also a regional problem for Southeast Asia and the Western Pacific countries. Using the same database for estimating the global scene, a 'notable increase in incidence was observed among males in the Western Pacific and females in Southeast Asia.' From 2010 to 2019, mortality rates did not increase in the Western Pacific, but 10.6% did so in Southeast Asia (24). EoCRC is most probably also prevalent in Thailand. Some interesting information could be obtained from the Khon Kaen province.

In the Nam Pong District, a screening trial of CRC using a fecal immunochemical test (FIT) covered the age range of 45 to 74 years (25). The research group published a paper to test adult height as a risk factor for CRC, which could not be confirmed. However, the results allow some speculation about the incidence of EoCRC around Khon Kaen province (26). The population-based cohort study recruited participants from 1990 to 2001 and recorded the CRC cases up to December 2020. From the cohort of 19.861 persons within the age range 30 to 49 years old at the time of enrollment, 39 (61/10.000) CRC cases were recorded from 6390 individuals, and 8020 persons aged 50 years and older, 79 (98,5/10.000) CRC cases were recorded. The age of those found finally with CRC is not given within the publication. At least it can be stated that 30% of the cases recorded derived from the population group aged 30 to 49 years old when entering the cohort.

A case-control study assessed 'modifiable' risk factors for CRC from 501 cases from 11 Thai provincial hospitals compared to 997 healthy individuals (27). Risk factors in Thailand don't differ from those already mentioned above, but family history had an extraordinary association with colon cancer risks.' The authors concluded that CRC 'might have a higher association with genetic factors '(it should be added also 'molecular factors') than behavioral ones.

The need for increasing research for EOC and EoCRC

The etiology of EOCs must be better understood and needs to be known for primary and secondary prevention. Early-onset against later-onset CRC is two different expressions of the disease when considering genetic and molecular factors. A summary of what needs to be known was published recently under the headline 'A common cancer at an uncommon age' (22). There are five critical areas to be addressed for investigating EoCRC biology. Besides molecular and genetic characterizations, single-cell and spatial transcriptomics should be examined in the tumor microenvironment. Especially besides environmental risk factors, a deeper insight into pathophysiology is necessary. Additionally, we should not forget to look into the gut macrobiotics.

The complicated genetic scenario around EoCRC - Lynch syndrome and 'repair genes'

Polyposis of the colon is a risk factor and can lead to CRC. Most of the EOC cases occur sporadic. About 2 to 4% of cancers don't occur sporadically but are hereditary because of DNA

mutation of four so-called ‘mismatch repair genes’ (MMR). The dysfunction of these genes is caused by the interference of a non-mismatch repair gene, the epithelial cellular adhesion molecule (EPCAM), which silences the MMR gene MSH2 expression. The faulty mechanism is known as Lynch syndrome. The MMR genes repair incorrect pairing of nucleotide bases during DNA replication. If the repair is not working correctly, the risk of cancer increases. Usually, two functional alleles (copies) of the gene are involved. Those borne with one of the alleles not functioning have the Lynch syndrome autosomal dominant inherited. First-degree relatives have a 50% chance of having Lynch syndrome as well (28).

‘Microsatellite instability’ and lack of methylation

The Lynch syndrome alone cannot explain the rise in the EoCRC (22). In a pooled analysis of 23 individual studies of sporadic EoCRC patients, only 10% had tumors where the MMR genes were involved (29, 30). Other repairing genes work against microsatellite instability in tumor DNA, such as BRAF (v-RAF murine sarcoma viral oncogene homolog B1), fixing a defective DNA mismatch, and need methylation for DNA repair. Methylation is a primary epigenetic mechanism. The faulty repair mechanism could not be found in EoCRC but only in the cohorts of older patients (31). Still, it might be that the likelihood of Lynch syndrome is higher in the group of EoCRC and goes down with older age since BRAF mutation and the mismatch repair deficiency increases with more senior age (30), but this leaves still 74% of EoCRC within a population-based cohort unexplained (29).

Next-generation sequencing

Another attempt to shed light on the genetic background is using the next-generation sequencing method, including genes encoding signaling pathways within oncogenic drivers. From those investigated, APC (keeps the cell from dividing and growing too fast) and BRAF were less detected in EoCRC, whereas TP53 (acts as a tumor suppressor) and β-catenin (CTNNBI) (works for stem cell renewal and organ regeneration) and faulty signaling pathways were often linked to EoCRC (32, 33). The results from a clinical study questioned the findings. A selection of 759 CRC patients were divided into three groups, namely 35 years and younger, 36 to 49 years, and 50 years and older. The tumors of the two groups of EoCRC were commonly left-sided and suffered from rectal bleeding and pain. Still, they were ‘otherwise clinically and gnomically indistinguishable’ from the group of older patients (34). Why this study could not even partly confirm the forgoing results obtained from three independent cohort studies (33) and analysis with 18.218 specimens (32) needs to be clarified.

‘Methylation’ is more common in older age

So far, the genetic scenario has not sufficiently explained the high association to the family hereditarily and the tumor location supposed to define EoCRC. To further explore the genetic background, epigenetics, and methylation are promising facets. The expression of the MMR gene MSH2 requires methylation for proper functioning. Methylation is one of the primary mechanisms for epigenetic phenomena. An epigenetic mechanism is heritable and caused by a mutation in the base-pair sequence of the DNA (35). Hypomethylation in the genetic circumstances available here is more common in the younger adults at risk for EoCRC compared

to older individuals (18, 36). The finding that at least three oncogenes silenced by methylation was discussed and might be interesting for further research concerning EoCRC (37).

Outlook

To work against EoCRC should be of significant interest to public health in its efforts to increase life expectancy in adults. Public health should focus on environmental risk factors such as nutrition and a physically active lifestyle and encourage secondary prevention by lowering the eligible age for EoCRC screening. At the same time, molecular biology, genetics, and epigenetics research might not usually be possible. One or the other population-based study, cooperating with laboratory scientists, would benefit both sides (38). Without an effort to understand and follow what is going on in genetic and biological research, public health is in danger of being unable to track significant developments within its fields of interest, being population health and the prevention of very common diseases.

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Frank P. Schelp is responsible for the manuscript's content, and the points of view expressed might not reflect the stance and policy of the Faculty of Public Health, Khon Kaen University, Thailand.

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