Rising cancer incidence in younger adults: is obesity to blame?

Published Online
February 4, 2019
http://dx.doi.org/10.1016/S2468-2667(19)30017-9

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Although cancer has historically been considered a disease of aging, a reported sharp rise in colorectal cancer incidence among adults aged 54 years and younger beginning in the mid-1980s for the colon and mid-1970s for the rectum[1] has motivated researchers to examine risk factors for early onset disease.[2] In *The Lancet Public Health*, Hyuna Sung and colleagues[3] report a rigorous and extensive analysis of data from 25 state cancer registries, in which they examined contemporary incidence trends for 30 cancers in the USA. This analysis, which included 14 672 409 incident cancers ascertained from registries covering 67% of the US population between Jan 1, 1995, and Dec 31, 2014, extends their previous work on colorectal cancer incidence.[1] The new study included 12 cancers considered to be related to obesity according to a 2016 report from a working group convened by the International Agency for Research on Cancer,[4] and 18 additional common cancers not designated as obesity-related in the same report. The investigators examined trends in incidence, based on annual percentage changes and incidence rate ratios, for each of the 30 cancer types by age and birth cohort.

The most striking finding was that cancer incidence appears to be rising disproportionately in younger adults (aged 25–49 years), and in consecutively younger birth cohorts for half of the cancers classified as obesity-related. These cancers include colorectal, corpus uteri, gallbladder, kidney, pancreatic, and multiple myeloma. Thyroid cancer, also considered to be obesity-related, showed markedly rising incidence in both younger and older adults. By contrast, only two of the other 18 cancers had similar trends of increasing incidence in younger adults. The investigators speculate that these findings are driven in part by the obesity epidemic, a hypothesis that is both provocative and plausible. As the investigators state, the prevalence of obesity in the USA more than doubled between 1980 and 2014,[5] providing compelling evidence that obesity could be a causal factor. However, despite the plausibility, the investigators' hypothesis and report have constraints that are important to consider.

First, the hypothesis assumes that cancer risk factors have a similar influence on cancer development across the lifespan. However, some early onset cancers can have a distinct cause from their later onset forms, as has been hypothesised for Hodgkin lymphoma[6] and well documented for breast cancer in women.[7] In general, most studies have investigated associations of obesity measured in adulthood with overall cancer risk, rather than associations of obesity in earlier life with early onset cancer risk. This method probably reflects that few studies have large enough populations for robust analyses of risk factors for early onset cancer—especially for the less common cancers highlighted in Sung and colleagues' report,[3] such as multiple myeloma and gallbladder cancer. Pooled analyses of multiple prospective studies will be required to characterise associations of risk factors with the early onset of most cancers, and to estimate latency for early life exposures. These considerations do not diminish the plausibility of the hypotheses discussed by Sung and colleagues; however, they do underscore the speculative nature of the investigators' interpretation and highlight the need for additional experimental and population-based studies that test the hypothesis more directly.

We find several additional aspects of the work by Sung and colleagues important to consider alongside the investigators' generally thoughtful discussion of their data. The first corresponds to inherent limitations of the International Agency for Research on Cancer working group report on which they based their approach. In particular, the report[4] acknowledged insufficient evidence regarding the association of obesity with some cancers grouped with the 18 additional cancers investigated by Sung and colleagues, including several for which emerging data strongly suggest a link (such as bladder cancer and diffuse large B-cell lymphoma).[8,9] Such cancers did not show temporal trends of increasing incidence in younger adults in Sung and colleagues' study.

Additionally, although the investigators diligently separated gastric cardia and non-cardia cancers for analysis, as well as HPV-related and HPV–unrelated oral and pharyngeal cancers, they chose to aggregate subtypes for other cancer types. These aggregated groups included non-Hodgkin lymphomas, comprising numerous aetiologically heterogeneous tumours,[10] and all lung cancers, all Hodgkin lymphomas, and all leukaemias except chronic lymphocytic leukaemia (which was appropriately grouped with the non-Hodgkin lymphomas). The interpretation of the data for

the aggregated groups is challenging; notably, the small number of subtype-specific findings presented in the appendix suggest moderate differences in age-specific and birth cohort-specific incidence across distinct subtypes of leukaemia and non-Hodgkin lymphoma.

Lastly, Sung and colleagues did not comment on why only some obesity-related cancers, and not all 12, showed temporal trends of markedly rising younger adult incidence, or why some obesity-related cancers appeared to have declining rather than increasing incidence in the older age groups. Such observations could reflect varying influences of other risk factors across such cancer types and age groups, and warrant further investigation. Despite these considerations and modest constraints, the report from Sung and colleagues yields timely insights. Importantly, the findings suggest the need for further close epidemiological monitoring of cancer incidence trends in younger adults and highlight the need for rigorous aetiological studies of exposures that could be responsible for the trends.

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We declare no competing interests.

1 Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017; **109**.
2 Liu PH, Wu K, Ng K, et al. Association of obesity with risk of early-onset colorectal cancer among women. *JAMA Oncol* 2018; published online Oct 11. DOI:10.1001/jamaoncol.2018.4280.
3 Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of population-based cancer registry. *Lancet Public Health* 2019; published online Feb 4. http://dx.doi.org/10.1016/S2468-2667(18)30267-6.
4 Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC working group. *N Engl J Med* 2016; **375:** 794–98.
5 Centers for Disease Control and Prevention. Prevalence of overweight, obesity, and extreme obesity among adults aged 20 and over: United States, 1960–1962 Through 2013–2014. 2016. https://www.cdc.gov/nchs/data/hestat/obesity_adult_13_14/obesity_adult_13_14.pdf (accessed Jan 5, 2019).
6 Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. *J Intern Med* 2008; **264:** 537–48.
7 Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA* 1997; **278:** 1407–11.
8 Sun JW, Zhao LG, Yang Y, Ma X, Wang YY, Xiang YB. Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. *PLoS One* 2015; **10:** e0119313.
9 Castillo JJ, Ingham RR, Reagan JL, Furman M, Dalia S, Mitri J. Obesity is associated with increased relative risk of diffuse large B-cell lymphoma: a meta-analysis of observational studies. *Clin Lymphoma Myeloma Leuk* 2014; **14:** 122–30.
10 Morton LM, Slager SL, Cerhan JR, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014; **2014:** 130–44.