Environmental health in the biology century: Transitions from population to personalized prevention

John D Groopman

Sidney Kimmel Comprehensive Cancer Center, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA
Corresponding author: John D Groopman. Email: jgroopm1@jhu.edu

Impact statement

There is a rapidly occurring, dynamic change, in the causes of morbidity and mortality in different populations across the globe. More people today are being diagnosed and treated for chronic diseases such as cancer, cardiovascular disease, and diabetes than ever before. Environmental exposures across the lifespan have a profound impact on the outcomes of these chronic diseases. Further, there are more people living today who have survived their therapy from these diagnoses and who are now differentially susceptible to environmental exposures. Collectively, this poses both the challenge and opportunity to the experimental biology and medicine community to build new models that reflect this changing human situation. The extraordinary advances in our understanding of the biology of disease provide extraordinary insights for both therapeutic and prevention strategies. Multidisciplinary teams including biological, physical, engineering and social and behavioral scientists will be needed to address this problem over the next several decades.

Abstract

Within the last decade, for the first time in human history, deaths from chronic diseases have exceeded mortality from acute causes worldwide. These chronic diseases encompass a spectrum of cancers, cardiovascular diseases, neurological diseases, and the emerging consequences of obesity and over nutrition. Further, there are more people today who are cancer survivors as well as people who are afflicted with multiple chronic diseases. This results in an emerging new group of susceptible populations with complex biology's that will drive the development of new experimental models. Since environmental exposures have a profound impact from the etiology of disease through progression and response to therapeutic and preventive interventions, a new appreciation of the role of environmental health has emerged. This mini-review will attempt to provide a global perspective on the transitions that have occurred in environmental health over the last 200 years and how these transitions are impacting diverse populations globally. The extraordinary advances in our understanding of the biology of normal development and the molecular progression of disease processes have created unprecedented opportunities for the translation of basic science to therapy and prevention. The need to integrate findings from the biological, physical, engineering, social, and behavioral sciences, sometimes called convergence, points to an imperative to develop new team science approaches to address the health consequences of environmental exposures. Finally, as it is increasingly recognized that disease outbreaks in one part of the world are no longer isolated from global impacts, there is a need to assure that our next generations of trained scientists have grounding in global collaborations.

Keywords: Epidemiology, carcinogenesis, biomarkers, cardiovascular, genotoxicity, medicine/oncology

***Experimental Biology and Medicine* 2019; 244: 728–733. DOI: 10.1177/1535370219837903**

Introduction

Over the past 150 years, the spectrum of illnesses affecting human populations across the globe has dramatically changed. This epidemiologic transition from acute to chronic disease dominance is mirrored by the remarkable upward trajectory in life expectancy, and this is a reflection of successful multidisciplinary efforts in the basic, applied, social and clinical sciences. As greater opportunities for the translation of our sciences that impact many acute diseases have occurred, a greater proportion of our populations are now at risk for chronic diseases such as the varied cancers, cardiovascular, diabetes and neurological afflictions. Further, in our most recent past, starting at the end of the 20th century, over nutrition and consequent diseases, such as diabetes, all reflecting the obesity epidemic are dramatically changing the substrate upon which environmental exposures become manifest. Collectively, while dramatic successes have occurred in the clinical management and cure of specific diseases our overall ability to design prevention strategies for populations that are at high risk for many different complex diseases remains a significant challenge for the future. This mini-review will provide a perspective on how environmental health plays a critical role in the transition from population-based prevention to personalized prevention that employs the translation of many of our basic science breakthroughs.

In this mini-review, a framework for the differences in environmental health challenges for the 19th, 20th and 21st centuries will be provided followed by an overview of population health during this timeframe and perspectives throughout the rest of the 21st century. There will be a specific case study that reflects the critical years starting in 1960 to 1975 that represented a watershed moment in the development of environmental health policies and regulations that have greatly impacted air, food, water, and soil exposure vectors. In this current century, the rapid development of personalized exposure monitoring, personalized therapy and the potential for personalized prevention is becoming deployed across many communities. As a paradigm for environmental health causality and opportunities for prevention, a discussion of the changes in liver cancer will be used as an illustration. Finally, several of the challenges for research community will be described as opportunities for the future.

Environmental health in the 19th, 20th and 21st centuries

The chemical, physical, and biological contributors to environmental health have proportionally changed over the past 200 years. A crude delineation can be framed by framing the 19th century as the century of chemistry, the 20th century as a century of physics and the 21st century as a century of biology (Figure 1). As always, great advances in each of these disciplines have had both positive and negative impacts on human health. In many instances, studies of chemistry, physics, and biology have led to remarkably rapid cures through therapeutic advances for many human ailments. In contrast, the legacy of a number of industries built upon these scientific fields have not only impacted workers and their families at the time of their exposures but have also contributed to long-term contamination that expose people to these risks over many decades later.

Scientific discovery during the 19th century propelled our understanding and abilities to manipulate chemical reactions that produced a wide array of organic and inorganic compounds. The organic chemistry revolution can be traced to a number of founder studies exemplified by William Perkin's synthesis of mouveine in the mid-1850s.[1] This triumph in organic chemistry led to the industrial scale synthesis of many synthetic dyes that were then employed in the textile industry. Since the modern analytical tools of mass spectrometry, spectroscopy, and other analytical cornerstones were far into the future at the time of these initial syntheses, the large scale, given the analytical methods of the time, at which these agents had to be produced immediately led to significant environmental contamination. The toxicological and biological consequences of this contamination would not be recognized for many decades. The explosion of the organic chemistry-based dye industries was rapidly exploited with the formation of many companies including BASF (Badische Anilin und Soda Fabrik), Bayer, IG Farben (Syndicate of Dyestuff industry Corp.). Worker exposure in these industrial facilities led to

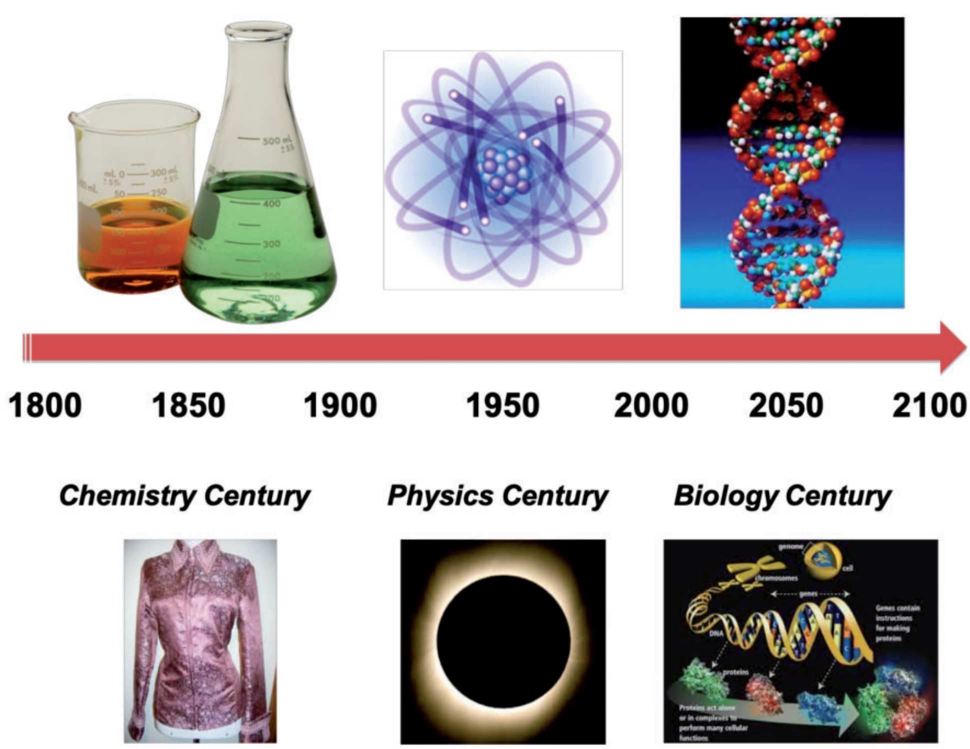

Figure 1. Time line of the chemistry, physics and biology centuries. (A color version of this figure is available in the online journal.)

a dramatic increase in a number of cancers, including bladder cancer, that propelled the occupational exposure field starting in the 1890s.[2] Indeed, some of the earliest insights into chemical agents causing human cancer came from these worker exposure situations where high exposure to these potent agents in a relatively small number of workers induced what were at that time very rare cancers.

By the early 20th century, there were many documented instances of workers developing heretofore rare cancers from exposures occurring in the workplace. However, as is often found in scientific development, the chemistry that led to the production of many dye compounds also produced some of the original antibiotics that have been of profound importance in saving many lives. In 1932, Gerhart Dogmak (Nobel Prize in Physiology or Medicine 1939) used Prontosil red, to treat his daughter who was desperately ill with a streptococcal infection.[3,4] She recovered and much of the organic chemical driven antibiotic revolution was initiated. Hundreds of millions of people have been treated with these drugs to great success. Further, these same synthetic methodologies also led to the development of a number of pesticides, herbicides, and insecticides that have been deployed for the eradication of organisms that contribute to many human diseases including malaria, yellow fever, schistosomiasis, and others. Collectively, these agents are all members of the persistent organic pollutants (POPs) that constitute major environmental concerns nearly 100 years after the original synthesis. A recent review of the International Agency for Research on Cancer (https://monographs.iarc.fr/), whose risk evaluations are a cornerstone in cancer risk assessment, shows the overwhelming majority of agents that cause cancer in people are direct descendants of this organic chemistry revolution of the 19th century.[5]

While the roots of the chemistry century started in the 1850s, the advances in physics very much dominate the 20th century. Wilhelm Rontgen was the first recipient of the Nobel Prize in physics in 1901 for his discovery of X-rays and their use in imaging, which had been reported only six years earlier. The initial manuscript of these discoveries was submitted for publication on 27 December 1895 and published the next day in the Proceedings of the Physico-Medical Society of Würzburg.[6] Perhaps no other scientific discovery was so rapidly translated into clinical practice than the X-ray imaging technology. Its deployment to characterize bone fractures and other injuries occurred over a matter of months and this had a profound impact on clinical practice. Unfortunately, within several years, workers such as Clarence Dally who was in Thomas Edison's laboratory succumbed to what was characterized as X-ray cancer.[7] While his death in 1904 might have been the first documented mortality case, it still took over 20 years for the International Commission on Radiation Units and Measurements (ICRU) to develop standards for radiation exposure to protect people from deleterious exposure. Thus, radiation has both positive therapeutic and negative health consequences, and ionizing radiation exemplified by X-rays represents one of the few examples where exposure and dose are identical. The radiation biology field that has evolved from these early investigations has been extremely influential in standardizing exposure and dose for spectrum of environmental agents.

Populations and population health in the 21st century

The demography of the planet has been changing very rapidly since the 19th century; in 2019, the four most populous countries are China, India, United States, and Indonesia (www.census.gov). Just 30 years in the future, the most populous countries in order will be India, China, United States and Nigeria. Very dramatically, the population in China will be plateauing while the population in Nigeria will have almost doubled in 30 years and is projected to double again by the end of the 21st century. In 2100, both India and China will have a total of 800 million fewer people due to the confluence of a lower birthrate and economic development not contributing to longer life expectancy. These data are all summarized in Figure 2. Thus, the demographics of our planet is about to dramatically change over the course of the century, and the population centers of Asia and South Asia in Africa will become the major fraction of people. This demographic change will challenge the broad prevention community to develop strategies to protect against avoidable disease risk factors.

Since the 1850s, survival in the first five years of life has increased remarkably.[8,9] In England, nearly 25% of males died before age 5 in the 1850s and now that fraction is extremely small, less than 0.4%. This success is then reflected in the overall increase in the fraction of people who live until and past age 75 at which time there is a nearly exponential increase in the proportion of individuals diagnosed with chronic diseases. Two examples in the United States that serve as guideposts for the future reflect the remarkable changes that have occurred in both cardiovascular disease and overall cancer mortality since 1970. In the United States, the overall death rate per hundred thousand for cardiovascular disease has decreased by nearly 45%.[10,11] Overall heart disease has decreased by 75% between 1969 and 2013. Overall cancer deaths in the United States from 1991 until the present has decreased rapidly such that there are nearly 2.5 million people who were projected to succumb from cancer in 1990 to the present did not because of the reduction in tobacco smoking.[12] Tobacco reduction use has also contributed greatly to the reduction in cardiovascular disease deaths along with a number of therapeutic agents that have reduced the impact of hypertension and arteriosclerosis. The successes seen in the United States are now being rapidly seen in other countries globally. While this is all good news, it is still clear that poverty and economic opportunities contribute to smaller successes in the reduction of overall mortality from environmental exposures.

The dramatic environmental pollution exposures seen in many urban areas during the mid-20th century contributed greatly to the demand for policy and regulations that strove to control these contaminants in both air and water. Legislation such as the clean air act contributed to the requirement for the reduction of air pollution. The World Health Organization (WHO) has provided analyses that

21st Century Population Statistics

2019		2050		2100	
1 China	1,382,920,713	1 India	1,807,878,574	1 India	1,551,612,713
2 India	1,315,379,910	2 China	1,437,161,948	2 China	941,079,910
3 USA	328,159,265	3 USA	420,080,587	3 Nigeria	730,812,035
4 Indonesia	263,271,879	4 Nigeria	356,544,098	4 USA	478,271,879
5 Brazil	207,939,227	5 Indonesia	313,020,428	5 Tanzania	316,739,227
6 Pakistan	196,242,560	6 Pakistan	294,995,104	6 Pakistan	261,242,560
7 Nigeria	191,269,059	7 Bangladesh	279,955,405	7 Indonesia	254,065,352
8 Bangladesh	163,065,352	8 Brazil	228,426,737	8 Congo	212,269,059
9 Russia	142,059,244	9 Congo	183,260,098	9 Philippines	178,059,244
10 Japan	126,763,244	10 Mexico	147,907,650	10 Brazil	177,063,244

- *Note: Data updated 8-8-2018*
- *Source: U.S. Census Bureau, International Data Base.*

Figure 2. Top 10 countries in population over time. (A color version of this figure is available in the online journal.)

upwards of 7 million people die each year from the impact of air pollution exposure.[5] Further, WHO concluded that 40% of ischemic heart disease, 40% of stroke, 11% of chronic obstructive pulmonary disease (COPD) and 6% of global lung cancer deaths are caused by outdoor air pollution. Indeed, in 2013, the International Agency for Research on Cancer (IARC/WHO) classified outdoor air pollution as a Group 1 known human carcinogen recognizing that this complex mixture, of which benzene is a significant contributor, has both anthropogenic and biogenic sources.[13]

The biology century and convergence

The 21st century is arguably the century of biology, and our understanding of biology is expanding at an extraordinary pace. The development of our understanding of basic biology was certainly accelerated by the characterization of the structure of DNA in 1953. The two decades that followed involved intensive studies at both the molecular and cellular level generally using prokaryotic systems as models. The next wave of investigations that started in the 1980s was propelled by rapid development of genomic sequencing technologies and the discovery of the polymerase chain reaction. This culminated with the initial drafts of the human genome that were reported at the start of the 21st century. All of these findings are now converging through the merging of life, engineering in physical sciences that will fundamentally change the approach to disciplinary strategies in human health and the global scale.[14,15] Public health practice in training will be greatly impacted by the need for multidisciplinary approaches to address the chronic diseases that will be the major sources of morbidity for the rest of the century.

Technologies built upon our genomic foundation include the new strategies that deploy Crispr, biologically directed engineering, the design of both genetically modified organisms and genetically edited organisms are changing the landscape of research strategies. As always, there will be both positive and negative consequences from these technologies and hopefully we will be able to be ahead of the curve in contrast to other technological advances that have already been described.

There is a revolution occurring that will continue to impact personalized exposure monitoring, therapy, and prevention. Much of this effort is encompassed in the exposome projects.[16] Personalized electronics, global positioning detection, and sensors that can contribute to individualized exposure assessment are rapidly emerging.[17,18] These were first deployed using accelerometers in order for people to monitor exercise but this is very rapidly expanding into many physiological and environmental measurements that can be integrated into health status assessment. The areas of personalized medicine, personalized prevention in personalized genomics are greatly expanding as each of these types of technological strategies become less expensive for the individual. The liquid biopsy is now becoming standard of care for the monitoring of patients following their cancer therapy in order to detect the earliest recurrence of disease that in turn can lead to the use of different therapeutic options.[19] The use of liquid biopsy to measure both DNA and protein molecules, better signatures of cancer development and risk, will continue to expand as basic discovery is made of these mechanistic processes. Similar strategies are now being deployed in fetal diagnosis due to the ability to measure fetal DNA in the maternal circulation that in turn can provide early insights into health concerns prior to birth.[20,21]

Liver cancer as a paradigm in environmental health

Collectively, liver cancer accounts for nearly 9% of all reported cancer deaths and is one of the most common causes of cancer mortality worldwide, http://gco.iarc.fr/.[22] The incidence of liver cancer varies enormously globally and unfortunately the burden of this nearly always fatal disease is much greater in the less economically developed countries of Asia and sub-Saharan Africa.[5] HCC is also the most rapidly rising solid tumor in the US and Central America and is overrepresented in minority communities, including African-Americans, Hispanic/Latino-Americans and Asian-Americans.[22–24] Overall, there are more than 850,000 new cases each year and more than 300,000 deaths annually in the People's Republic of China (P.R.C.) alone.[5] In contrast with most common cancers in the economically developed world where over 90% of cases are diagnosed after the age of 45, in high-risk regions, liver cancer onset begins to occur in both men and women by 20 years of age and peaks between 40 and 49 years of age in men and between 50 and 59 years of age in women.[25–27] This earlier onset of HCC might be attributable to exposures that are both substantial and persistent across the life span. Gender differences in liver cancer incidence have also been well described, and worldwide the number of cases among men were 554,000 and 228,000 among women in 2012.[28] These epidemiologic findings are also reflected in experimental animal data for one potent liver carcinogen linked to human HCC, aflatoxin, where male rats have been found to have an earlier onset and higher incidence of cancer compared to female animals.[29] Thus, the consistency of the experimental animal and human data points to the important role that environmental exposures play in gender differences in HCC risk.

To date, the significant etiological factors associated with the development of HCC have been defined by biomarker studies and they are infection in early life with hepatitis B virus (HBV) and lifetime exposure to high levels of aflatoxin B_1 (AFB_1) in the diet.[30,31] Over the past 25 years, an appreciation for the role of the hepatitis C virus (HCV) has also emerged. HCV is contributing to HCC being the most rapidly rising solid tumor in the US and Japan.[32] Detailed knowledge of the etiology of HCC has spurred many mechanistic studies to understand the pathogenesis of this nearly always-fatal disease.[30,33,34] Fortunately, the successful development and deployment of some highly effective new drugs that cure HCV infection is a major advance and will hopefully diminish the role of this virus in liver cancer.[35,36]

Alcohol is a recognized human carcinogen and has been causally linked to HCC. Alcoholic cirrhosis and heavy alcohol use have been repeatedly associated with an increase in HCC risk.[37] However, it is unclear if alcohol use in the absence of cirrhosis influences HCC development.[38] Several studies have demonstrated an increased risk of HCC up to 5-fold with consumption of more than 80 g of alcohol per day or approximately 6–7 drinks per day.[37] The risk of HCC ranges from borderline statistically significant to more than two-fold with chronic alcohol consumption of less than 80 g/day.[37] A synergism between alcohol and HBV and HCV infections has also been described.[37,39]

In addition to the association of alcohol and HCC, in economically developed countries the dramatic rise in overweight and nonalcoholic fatty liver disease has also been related to increased HCC.[40–42] Of major concern for the future are the role that obesity, diabetes, and general underlying fatty liver disease will play in the development of liver cancer.[43–45] While the historic risk factors for liver cancer described above are addressed through a spectrum of prevention methods, these new etiologic factors portend an increasing trajectory in the incidence of this disease. Both therapeutic and pre-disease interventions will need to be deployed now to blunt the impact of these risk factors in the decades to come. Collectively, the development and validation of a new generation of biomarkers reflecting complex processes such as inflammation will need to be deployed.

The challenge

There are major challenges ahead of us for the translation of our basic science findings to improving the health status of populations over the next century. An example of one of those challenges using cancer as a model is the recognition that only 10% of the biology development occurs following the diagnosis of the cancer. Ninety percent of that biology occurs prior to diagnosis and that provides the opportunity for the development of prevention and its interventions.[46] We also need to recognize that there are many regulations, policies and interventions that have been successfully used over the last century that improved the public health. These include legislation from the clean air act and other progressive policies that have saved many lives.[47] Collectively, the deployment of science has been extremely positive and one of the best examples is the extrapolation of science from initial hypotheses that reflected concern over stratospheric ozone depletion through the use of chlorofluorocarbon propellants. We are well on the way to seeing a healing of the ozone hole through the banning of these types of compounds. We should recall it was 50 years ago when we got our first visualization of the blue planet from the perspective of astronauts orbiting the moon that collectively we realized that this was the only environment we had and it was a call to challenge us to solve the solutions on our planet in order to assure the improvement of everyone's health.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

Support for the work was provided in part by NIH Grant from the National Cancer Institute, Comprehensive Cancer Center Core Grant, 5 P30 CA006973.

REFERENCES

1. Ball P. Chemistry: Perkin, the mauve maker. *Nature* 2006;**440**:429
2. Michaels D. When science isn't enough: Wilhelm Hueper, Robert A. M. Case, and the Limits of Scientific Evidence in Preventing Occupational Bladder Cancer. *Int J Occup Environ Health* 1995;**1**:278–88
3. Iyer HV. History revisited-Prontosil red. *J Emerg Med* 2008;**35**:209–10
4. Chung KT. Azo dyes and human health: a review. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2016;**34**:233–61
5. Stewart BW, Wild CP (eds) World Cancer Report 2014. Lyon: International Agency for Research on Cancer, 2014.
6. Babic RR, Stankovic Babic G, Babic SR, Babic NR. 120 Years since the discovery of X-rays. *Med Pregl* 2016;**69**:323–30

7. Brown P. American martyrs to radiology. Clarence Madison Dally (1865–1904). 1936. *AJR Am J Roentgenol* 1995;**164**:237–9
8. Peto R. Harveian Oration 2012: halving premature death. *Clin Med (Lond)* 2014;**14**:643–57
9. Norheim OF, Jha P, Admasu K, Godal T, Hum RJ, Kruk ME, Gomez-Dantes O, Mathers CD, Pan H, Sepulveda J, Suraweera W, Verguet S, Woldemariam AT, Yamey G, Jamison DT, Peto R. Avoiding 40% of the premature deaths in each country, 2010–30: review of national mortality trends to help quantify the UN sustainable development goal for health. *Lancet* 2015;**385**:239–52
10. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, Mussolino ME, Hsu LL, Addou E, Engelgau MM, Gordon D. Decline in cardiovascular mortality: possible causes and implications. *Circ Res* 2017;**120**:366–80
11. Roth GA, Johnson CO, Abate KH, Abd-Allah F, Ahmed M, Alam K, Alam T, Alvis-Guzman N, Ansari H, Arnlov J, Atey TM, Awasthi A, Awoke T, Barac A, Barnighausen T, Bedi N, Bennett D, Bensenor I, Biadgilign S, Castaneda-Orjuela C, Catala-Lopez F, Davletov K, Dharmaratne S, Ding EL, Dubey M, Faraon EJA, Farid T, Farvid MS, Feigin V, Fernandes J, Frostad J, Gebru A, Geleijnse JM, Gona PN, Griswold M, Hailu GB, Hankey GJ, Hassen HY, Havmoeller R, Hay S, Heckbert SR, Irvine CMS, James SL, Jara D, Kasaeian A, Khan AR, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Lal D, Larsson A, Linn S, Lotufo PA, Magdy Abd El Razek H, Mazidi M, Meier T, Mendoza W, Mensah GA, Meretoja A, Mezgebe HB, Mirrakhimov E, Mohammed S, Moran AE, Nguyen G, Nguyen M, Ong KL, Owolabi M, Pletcher M, Pourmalek F, Purcell CA, Qorbani M, Rahman M, Rai RK, Ram U, Reitsma MB, Renzaho AMN, Rios-Blancas MJ, Safiri S, Salomon JA, Sartorius B, Sepanlou SG, Shaikh MA, Silva D, Stranges S, Tabares-Seisdedos R, Tadele Atnafu N, Thakur JS, Topor-Madry R, Truelsen T, Tuzcu EM, Tyrovolas S, Ukwaja KN, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Weintraub R, Wolfe C, Workicho A, Xu G, Yadgir S, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Zaidi Z, Zaki MES, Zipkin B, Afshin A, Gakidou E, Lim SS, Mokdad AH, Naghavi M, Vos T Murray CJL. The burden of cardiovascular diseases among US states, 1990–2016. *JAMA Cardiol* 2018;**3**:375–89
12. Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, Henley SJ, Holtzman D, Lake A, Noone AM, Anderson RN, Ma J, Ly KN, Cronin KA, Penberthy L, Kohler BA. Annual report to the nation on the status of cancer, 1975–2012, featuring the increasing incidence of liver cancer. *Cancer* 2016;**122**:1312–37
13. Loomis D, Grosse Y, Lauby-Secretan B, Ghissassi FE, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K. The carcinogenicity of outdoor air pollution. *Lancet Oncol* 2013;**14**:1262–3
14. Sharp P, Hockfield S. Convergence: the future of health. *Science* 2017;**355**:589
15. Sharp PA, Langer R. Research agenda. Promoting convergence in biomedical science. *Science* 2011;**333**:527
16. Dennis KK, Marder E, Balshaw DM, Cui Y, Lynes MA, Patti GJ, Rappaport SM, Shaughnessy DT, Vrijheid M, Barr DB. Biomonitoring in the era of the exposome. *Environ Health Perspect* 2017;**125**:502–10
17. Kim DH, Lu N, Ma R, Kim YS, Kim RH, Wang S, Wu J, Won SM, Tao H, Islam A, Yu KJ, Kim TI, Chowdhury R, Ying M, Xu L, Li M, Chung HJ, Keum H, McCormick M, Liu P, Zhang YW, Omenetto FG, Huang Y, Coleman T Rogers JA. Epidermal electronics. *Science* 2011;**333**:838–43
18. Swager TM. Sensor technologies empowered by materials and molecular innovations. *Angew Chem Int Ed Engl* 2018;**57**:4248–57
19. Mader S, Pantel K. Liquid biopsy: current status and future perspectives. *Oncol Res Treat* 2017;**40**:404–8
20. Yu SC, Chan KC, Zheng YW, Jiang P, Liao GJ, Sun H, Akolekar R, Leung TY, Go AT, van Vugt JM, Minekawa R, Oudejans CB, Nicolaides KH, Chiu RW, Lo YM. Size-based molecular diagnostics using plasma DNA for noninvasive prenatal testing. *Proc Natl Acad Sci USA* 2014;**111**:8583–8
21. Skrzypek H, Hui L. Noninvasive prenatal testing for fetal aneuploidy and single gene disorders. *Best Pract Res Clin Obstet Gynaecol* 2017;**42**:26–38
22. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;**136**:E359–86
23. American Cancer Society. Cancer facts and figures. 2005;**2005**:22–7
24. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? *Hepatology* 2014;**60**:1767–75
25. Chen JG, Zhu J, Parkin DM, Zhang YH, Lu JH, Zhu YR, Chen TY. Trends in the incidence of cancer in Qidong, China, 1978–2002. *Int J Cancer* 2006;**119**:1447–54
26. Vatanasapt V, Martin N, Sriplung H, Chindavijak K, Sontipong S, Sriamporn S, Parkin DM, Ferlay J. Cancer incidence in Thailand, 1988–1991. *Cancer Epidemiol Biomarkers Prev* 1995;**4**:475–83
27. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**:74–108
28. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;**65**:87–108
29. Wogan GN, Newberne PM. Dose-response characteristics of aflatoxin B1 carcinogenesis in the rat. *Cancer Res* 1967;**27**:2370–6
30. Kensler TW, Qian GS, Chen J, Groopman JD. Translational strategies for cancer prevention in liver. *Nat Rev Cancer* 2003;**3**:321–9
31. Block TM, Mehta AS, Fimmel CJ, Jordon R. Molecular viral oncology of hepatocellular carcinoma. *Oncogene* 2003;**22**:5093–107
32. Tanaka V, Hanada K, Mizokami M, Yeo AET, Shih JWK, Gojobori T, Alter HJ. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. *Proc Natl Acad Sci USA* 2002;**99**:15584–9
33. Kensler TW, Egner PA, Wang JB, Zhu Y, Zhang BC, Lu PX, Chen JG, Qian GS, Kuang SY, Jackson PE, Gange SJ, Jacobson LP, Munoz A, Groopman JD. Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas. *Gastroenterology* 2004;**127**:S310S8.
34. Groopman JD, Kensler TW, Wild CP. Protective interventions to prevent aflatoxin-induced carcinogenesis in developing countries. *Annu Rev Public Health* 2008;**29**:187–203
35. Stasi C, Silvestri C, Voller F, Cipriani F. The epidemiological changes of HCV and HBV infections in the era of new antiviral therapies and the anti-HBV vaccine. *J Infect Public Health* 2016;**9**:389–95.
36. Barth H. Hepatitis C virus: Is it time to say goodbye yet? Perspectives and challenges for the next decade. *WJH* 2015;**7**:725–37
37. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology* 2004;**127**:S87–96
38. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;**127**:S35–50
39. Singal AK, Anand BS. Mechanisms of synergy between alcohol and hepatitis C virus. *J Clin Gastroenterol* 2007;**41**:761–72
40. Takamatsu S, Noguchi N, Kudoh A, Nakamura N, Kawamura T, Teramoto K, Igari T, Arii S. Influence of risk factors for metabolic syndrome and non-alcoholic fatty liver disease on the progression and prognosis of hepatocellular carcinoma. *Hepatogastroenterology* 2008;**55**:609–14
41. Ohki T, Tateishi R, Sato T, Masuzaki R, Imamura J, Goto T, Yamashiki N, Yoshida H, Kanai F, Kato N, Shiina S, Yoshida H, Kawabe T, Omata M. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. *Clin Gastroenterol Hepatol* 2008;**6**:459–64
42. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 2007;**37**:S88–94
43. Khan FZ, Perumpail RB, Wong RJ, Ahmed A. Advances in hepatocellular carcinoma: Nonalcoholic steatohepatitis-related hepatocellular carcinoma. *WJH* 2015;**7**:2155–61
44. Saran U, Humar B, Kolly P, Dufour JF. Hepatocellular carcinoma and lifestyles. *J Hepatol* 2016;**64**:203–14
45. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis* 2015;**19**:223–38
46. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr, Kinzler KW. Cancer genome landscapes. *Science* 2013;**339**:1546–58
47. Samet JM, Burke TA, Goldstein BD. The trump administration and the environment – heed the science. *N Engl J Med* 2017;**376**:1182–8