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ESSAY

Enigmas, priorities and opportunities in cancer epidemiology

Hans-Olov Adami[1,2,3] · **Olof Nyrén**[1]

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Introduction

As authors, we have several features in common: a long background as practicing surgeons; a decision to abandon clinical work because ultimately cancer epidemiology—a realm we entered haphazardly—appeared more exciting; and a conviction that our many years as practicing surgeons have served our life in science well as an inexhaustible source of curiosity, hypotheses and wonder at Mother Nature's many secrets and the challenging task to uncover them.

Now that we are both Emeritus Professors, it seems timely not to celebrate victories, but rather to summarize some of the many enigmas we stumbled upon without solving them, to critically review some of the directions our discipline has taken during the last decades, and to outline promising avenues for future research. We do so because prevention remains the most attractive, effective and perhaps realistic approach to cancer control. But progress in cancer prevention requires scientific discoveries, innovation and risk taking.

✉ Hans-Olov Adami
hadami@hsph.harvard.edu

[1] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, P.O.B 281, 171 77 Stockholm, Sweden

[2] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[3] Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Oslo, Norway

Enigmas

For some cancer sites, such as lung, liver and cervix, our etiologic knowledge is so advanced, and the causes are so preventable, that behavioral, implementation and policy research rather than etiologic research needs prioritization. Above all, we need political will and forceful action. If we were able to eliminate tobacco—a perverse commercial product that indiscriminately kills one out of two users—reduce alcohol abuse and implement universal vaccination against hepatitis B and oncogenic human papillomaviruses (HPV), then available evidence suggests that we would indeed ultimately eliminate a substantial proportion of the current global cancer burden.

But for too many cancer sites, the predominant causes remain elusive and prevention therefore continues to be beyond reach. During many years as scholars, we have indeed—often together and with no success—struggled with these enigmas, some of which are briefly outlined below. This list of enigmas could be easily expanded, indicating that important discoveries are waiting for creative individuals to break new ground. But we share a concern that the pace of discovery is slowing down rather than accelerating, a fate that probably applies to medical research in general [1]. And that harvesting the low-hanging fruits remains more attractive to many cancer epidemiologists—young and old—than to leave the comfort zone, enter new territory and undertake long-term, high-risk projects attacking deep and complex questions. This lack of boldness is attributable not only to personal shortcomings of single researchers, but also to funding agencies' inclination to support mostly short-term projects rather than the truly large undertakings. Only brave approaches may finally bring epidemiologists on stage to receive the Nobel Prize [2].

Gender disparities

With surprising consistency, the age-specific incidence of site-specific cancer is higher in men than in women, with only three notable exceptions: cancers of the thyroid, gall bladder and anus, which are more common in women. In a recent global assessment of this phenomenon we found that cancer incidence was statistically significantly higher in men than in women at 32 of 35 sites, with disparities greater than twofold for 15 sites and greater than fourfold for five sites. The consistency of the sex ratio over calendar time, among geographic areas and across GDP-groups as well as ethnic groups, is intriguing [3].

For 13 cancer sites the disparity is attributable to a documented higher prevalence of exposure to established cancer causes among men. Alcohol, tobacco smoking and occupational exposures are predominant. But for the majority of cancer sites, existing knowledge provides no conclusive explanation for the gender disparity. We acknowledge the substantial challenges in attacking this enigma. But if the causes of sex disparities were revealed and could be eliminated, about one-third of all stomach cancers, 28% of rectal cancer and 17% of all non-Hodgkin lymphomas would be prevented, as well as many other cancers with an unexplained male preponderance [3].

Esophageal cancer enigmas

Epidemiologic research has successfully revealed numerous risk factors for esophageal cancer and established distinct etiologies—with essentially no overlap—of the two main histopathologic types, squamous cell cancer and adenocarcinoma. In western populations, heavy alcohol consumption combined with smoking addiction is associated with a more than 20-fold excess relative risk of esophageal squamous cell cancer. And the excess relative risk of esophageal adenocarcinoma is of the same magnitude following long-term and severe gastroesophageal reflux, with a substantial additive effect of obesity [4]. But each of these distinct malignant phenotypes harbors profound epidemiologic enigmas.

It has been known for almost 50 years that esophageal squamous cell cancer occurs endemically in the inner Asian continent, with hotspots in Iran and China exhibiting incidence rates up to 100 times higher than in low-risk western populations. In these hotspots, instead of the three to fourfold male predominance seen in western populations—attributed mainly to historically higher prevalence proportions of smoking and alcohol use among men compared with women—the male/female ratio varies between 1:1 and 2:1, and the relative risks associated with smoking and alcohol use are typically less than two. Although less detailed information is available, a similar esophageal cancer belt exists in eastern sub-Saharan Africa, extending down to South Africa. In fact, cancer registers in Malawi and South Africa report a lifetime absolute risk of esophageal cancer among men that is considerably higher even than in the notoriously high-incidence Golestan Province, Iran [5], and in stark contrast to the rest of Africa. Interestingly, in eastern Africa, the male/female ratio is also as low as 1.5:1 [6].

Repeated, serious efforts to understand the causes of the striking excess of esophageal squamous cell cancer in Iran and China have so far been largely unsuccessful [4]. Nonetheless, reductions in incidence observed in these hotspots (by >2% per year) [7, 8] clearly indicate that modifiable environmental factors have been in operation. Factors linked to a low socioeconomic status and a family history of esophageal cancer are the strongest and most consistent risk factors in the Asian hotspots, suggesting interactions between susceptibility genes and correlates of low socioeconomic status. Nutritional deficiencies might seem plausible, but it has been remarkably difficult—despite numerous observational studies as well as randomized intervention trials—to unambiguously determine the nature of such deficiencies [4].

An alternative explanation could be an infection of some kind; recent studies have implicated poor oral hygiene [9, 10], gastric atrophy [11] (with a scope for gastric colonization of a broad range of microorganisms) [12], and—with an unusually strong signal—contacts with ruminant animals [13]. Epidemiologists and basic scientists should increase their efforts to identify plausible microbial suspects, and then go back to the field to test their hypotheses in appropriately designed epidemiological studies.

In the past, esophageal adenocarcinomas accounted for no more than a minute fraction of all esophageal cancers. But towards the end of the twentieth century an almost epidemic increase (in relative terms) occurred. With considerable geographic variation in magnitude and timing, we found a consistent increase in incidence between 1960 and 1990. The average annual increase ranged from 3.5% in Scotland to 8.1% in Hawaii, with similar proportional increase among men and women, but a maintained three to sixfold higher incidence among men. We also found that the onset of the epidemic varied considerably even between neighboring countries such as Sweden and Norway [14]. An increasing prevalence of established risk factors does not convincingly explain this upward trend. For instance, while the obesity epidemic began earlier in the US than in the UK, the start of the adenocarcinoma epidemic in the UK seems to have preceded that in the US by around two decades. A shift in classification of tumors near the esophagogastric junction has been practically ruled out as an explanation.

The incidence pattern, with abrupt rises taking place at different points in time (but similar for men and women) in

different countries, is consistent with the wide introduction, country by country, of a strong causal factor. The epidemic at first seemed to be confined to western countries, but there are indications that esophageal adenocarcinomas are now on the rise also in historical strongholds of squamous cell carcinoma such as Iran's Golestan Province [15] and China [16]. Hence, novel and resolute approaches are needed to reveal the causes of this upsurge, implement preventive measures and ultimately turn the tide. The goal of primary prevention is especially important because therapeutic progress remains slow, if any, for this highly fatal malignancy.

Stomach cancer paradoxes

The discovery of *Helicobacter pylori* (*H. pylori*) as a cause of peptic ulcer and stomach cancer clearly fulfills the criteria of a paradigm shift. This discovery also illustrates that scientific breakthrough arises when unconventional thinking, open-mindedness and luck work together, rather than as a consequence of strategic prioritization, career planning and dreams of quick successes. But the story of stomach cancer and *H. pylori* also offers two fascinating paradoxes.

Firstly, already a century before *H. pylori* was discovered, the incidence of stomach cancer—until recently the global leader among malignancies—began to decline in the majority of countries with reliable cancer registration and more recently also in Japan [17]. This "unplanned triumph" in cancer control was not of trivial magnitude; following a birth cohort pattern, Swedes born around 1960 had a 93% reduced risk compared with those born around 1910 [18]. Cross-sectional seroprevalence statistics, combined with limited prospective data indicating a narrow open window during childhood and adolescence when *H. pylori* infection is typically contracted, strongly suggest a birth-cohort-wise decline in the prevalence of the infection in western populations. However, the evidence is only circumstantial, and whether or not the timing of the postulated decline fits with the timing of the drop in stomach cancer incidence, taking into consideration an induction period of several decades, remains uncertain.

Despite the still continuously falling seroprevalence proportions, the incidence of stomach cancer might again be on the rise in low-risk western populations [19, 20]. Hence, although current or previous *H. pylori* infection might be a necessary cause of stomach cancer, other important factors are, no doubt, also in operation. Most likely such factors strongly modify the carcinogenicity of *H. pylori*, which is only partly understood. While eradication—or better, prevention—of the infection would seem to predict stomach cancer prevention, the success of intervention trials of *H. pylori* eradication in adulthood in terms of preventing stomach cancer has so far been disappointingly meagre. Failure to convincingly demonstrate any major effect could conceivably—at least partly—be explained by large subgroups of infected individuals being at low risk of stomach cancer. Therefore, identification of component causes and effect-modifying factors could lead to better risk stratification and overall better efficiency of prevention programs. Further, a better understanding of the transmission of *H. pylori*, notably why the probability of transmission has fallen under the critical level, below which the prevalence decreases, might be translated into programs for prevention of the infection.

The relation between peptic ulcer disease and subsequent risk of stomach cancer offers a second, related paradox [21]. *H. pylori* infection appears necessary for the development of ulcer disease, both in the stomach and duodenum. Hence, given the strong link between *H. pylori* infection and stomach cancer, all patients with ulcer disease would be expected to have a high risk of stomach cancer. But the relative risk of stomach cancer differs drastically between patients with an ulcer in the duodenum rather than the stomach; in the latter case it is increased almost twofold, as expected, whereas it is permanently reduced by 40% in the former [21]. *H. pylori* strains with different oncogenic potential might determine the location of the ulcer disease—or perhaps the effect of *H. pylori* is modified by some other intrinsic or extrinsic factor. Both theories await proper scientific testing. And the results might be profoundly important not only for biological understanding, but also for rational primary prevention through *H. pylori* eradication or prevention, which would be unjustified—or even risk-increasing—for some strains, or some combinations of causal factors, hypothetically associated only with duodenal ulcer.

Colorectal cancer becoming endemic in Norway

In the light of its high incidence and relatively favorable prognosis, colorectal cancer should be easily amenable for epidemiologic investigation. Yet, the number of established causes remains limited. Even for diet, one of the prime suspects, the lack of consistent associations is surprising among large, prospective and well-conducted epidemiologic studies [22]. Although genetic factors undoubtedly play a role [23], they cannot account for striking temporal trends and are unlikely to explain the substantial geographic variation in the incidence of this malignancy.

Among the Nordic countries, Denmark had the highest incidence—and indeed one of the highest in the world—during several decades after the beginning of cancer registration in the mid-twentieth century. Incidence was lowest in Finland and intermediate in Norway and Sweden, with modestly increasing temporal trends in all four

countries (Fig. 1) [24]. Since around the 1960s (when cancer registration was fairly complete in all Nordic countries) the age-standardized incidence has increased by about 18% in Denmark, 60% in Finland and 42% in Sweden. But in Norway, it soared by 250% with no evidence of leveling off. This trend can have arisen only following a dramatic increase in exposure to one or several causes, old or new, of colorectal cancer during the middle and latter half of the twentieth century.

This shift in exposure prevalence has generated thousands of excess colorectal cancer cases and deaths in Norway. Any similar increase in a deadly non-malignant disease—let alone an outbreak of a lethal infectious disease—would likely have been considered alarming and generated a loud call for public health action. But to the best of our knowledge, no resolute initiative has been undertaken to explain and prevent this Norwegian epidemic of colorectal cancer. Thus, a formidable challenge and opportunity for discovery is waiting for action from the international epidemiologic community.

Testicular cancer and descriptive epidemiology as a benchmark

Fortunately, testicular cancer—a rare malignancy overall but in many populations the most common among young and middle-aged men—has become highly curable. Yet, prevention of this malignancy would be even better, given that it would eliminate stigma and the burdening side-effects and long-term sequelae of radiation and chemotherapy. For few other malignancies does causal understanding appear to be so within reach, yet so elusive. One epidemiologic study after another has failed to extend the list of established causes beyond cryptorchidism and a positive family history. Although the hereditary component of testicular cancer appears stronger than for most other malignancies [25], the descriptive epidemiology convincingly documents a profound impact of environmental, potentially modifiable causes. We have indeed devoted repeated brainstorming sessions to generate promising testable causal hypotheses, but failed blatantly. We hope, therefore, that a new generation of cancer epidemiologists will embrace the concept that the descriptive epidemiology of testicular cancer offers a powerful benchmark for etiologic hypotheses.

The salient descriptive features of testicular cancer epidemiology include the following: a tenfold variation in incidence, respecting national borders with surprising consistency, even between countries in the relatively restricted Baltic area [26]; an increasing temporal trend that follows a birth cohort pattern [27] and has lasted for many decades; and an arrest of the increasing trend for birth cohorts in Baltic countries least affected by the Second World War, but not countries where the war took place [27]. The birth cohort pattern and the incidence peak already around age 30 further indicate that the etiologically relevant period is early in life, perhaps already in utero. Hence, one or several causal exposures, affecting entire populations [26], increased dramatically over time to generate an about 2–5% annual growth in incidence. The level of exposure appears to vary substantially between the otherwise homogenous Nordic populations, which feature a more than twofold variation in incidence (Fig. 2).

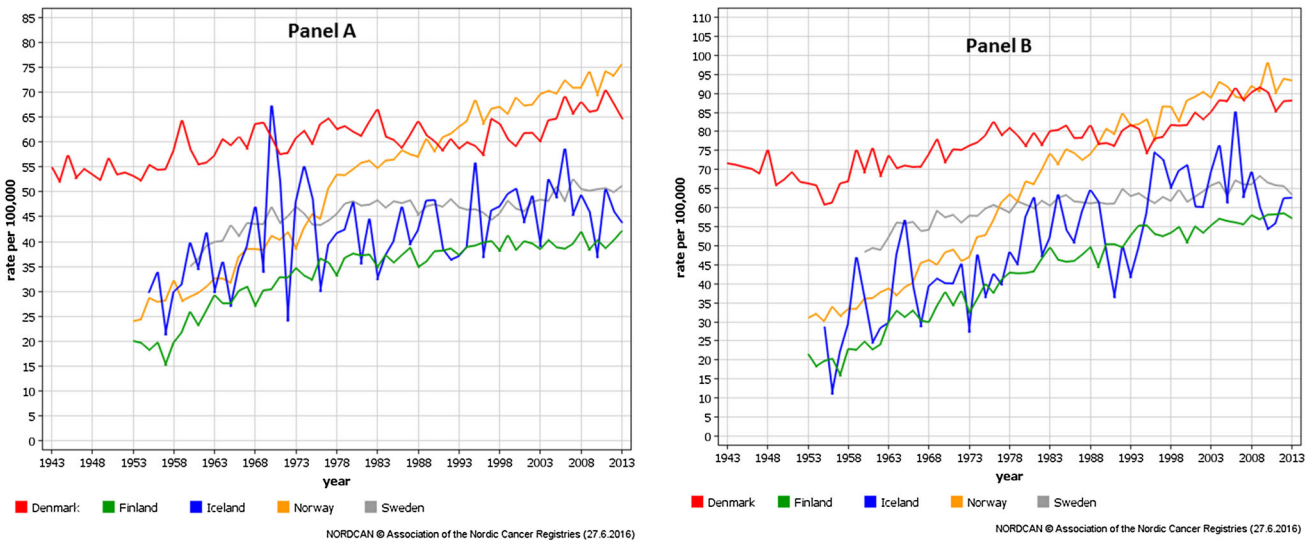

Fig. 1 Temporal trends in age-standardized incidence of colorectal cancer among women (Panel A) and men (Panel B) in the Nordic countries

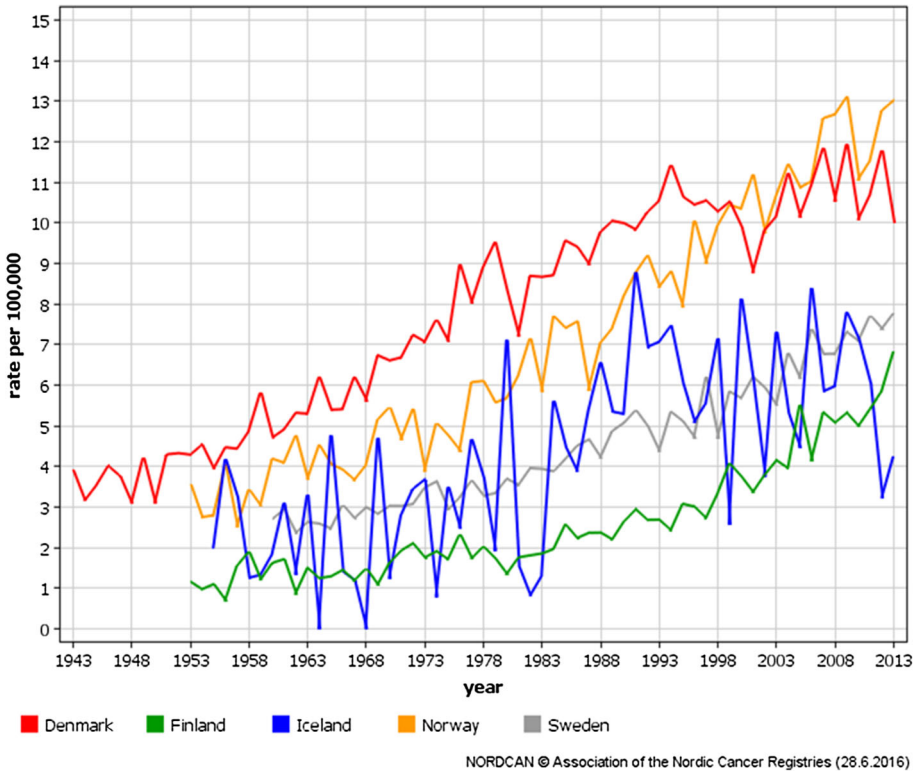

Fig. 2 Temporal trends in age-standardized incidence of testicular cancer in the Nordic countries

Priorities

Visionary foresight led Sir Richard Doll to initiate the prospective British Doctors' Study in 1951. A role model for countless subsequent cohort studies around the world, the long-term monitoring and elegant analyses of smoking habits among doctors in Britain have probably taught us more about the potential power of epidemiologic investigation and the disastrous health effects of tobacco use than any other study. Yet, until the 1980s, causes of human cancer were investigated chiefly in case–control studies, often of moderate size and many hospital- rather than population-based. Since then, with the initiation of the Nurses' Health Study at Harvard in 1976 as a landmark, we have witnessed an increasing prioritization of cohort studies at the expense of case–control studies. Subsequently, we have seen exponential growth in the emphasis on genetic studies and the search for informative biomarkers of exposure, early malignant transformation and phenotypic heterogeneity among cancer sites and types. In our view, it has become timely to critically review these developments and perhaps re-define the future direction and priorities in cancer epidemiology.

Why not case–control studies?

During the last decades, the case–control study has become increasingly dismissed because allegedly bias and confounding make results untrustworthy. And we agree wholeheartedly that the number of substandard case–control studies is staggering: underpowered, poorly designed, plagued by low participation among eligible cases and particularly controls, reliant on crude exposure assessment, insufficiently controlled for confounding, and analyzed with no prior plan, thereby entailing spurious findings and over-interpretation. We also acknowledge that undertaking a high-quality case–control study is challenging for many reasons. The theoretical framework may appear misleadingly simple but is in fact highly sophisticated; willingness to participate in epidemiologic studies has declined in many populations over time; and in some circumstances—such as occupational studies—proper assessment of exposures and confounders may be extremely difficult.

These difficulties notwithstanding, we believe that a new emphasis on case–control studies is justified—with the important spin-off effect that the coming generations of epidemiologists must not be methodologically handicapped by having hands-on experience only with cohort studies. There are three main reasons for our proposal. First, many malignant diseases are so rare that they become neglected in cohort studies because the number of incident cases accrued is never sufficient to allow analyses with adequate statistical power. Second, many causal hypotheses are, or should be, so specific and require such detailed exposure assessment that no multi-purpose cohort study can accommodate the needs. Salient examples include the role

of sexual practices and HPV infection in anal cancer [28] and of gastroesophageal reflux in adenocarcinoma of the esophagus [29]. Finally, we believe that high-quality case–control studies can still be undertaken—in particular if they are nested in existing or virtual cohorts where biological samples have been taken before development of symptoms [30]. Although less costly than large prospective cohort studies, high-quality case–control studies still require substantial resources, extensive planning, training of personnel and continuous effort during the entire fieldwork phase to monitor quality indicators, maintain high standards, train and motivate data collectors, increase participation rate among cases and controls, and otherwise ensure methodological rigor. [31]. Unless we can embrace these challenges, many opportunities will be lost, numerous discoveries will never see the light of day, and the etiology of many cancer sites will remain obscure.

The basic research misconception

No sensible scholar would argue against basic research as the central engine for discovery, biologic understanding, shift in paradigm, creation of new diagnostic and therapeutic technologies—and ultimately improving our understanding of how humans are constructed and function when they are healthy or ill. Yet, it is virtually impossible to work, as we have done for decades, in faculty committees, academies, awards assemblies, funding organizations and study sections—or having conversations with colleagues from the laboratory—without experiencing the misconception advanced by basic researchers that only experimental laboratory research—as opposed to human clinical or epidemiologic research—is "real" science, construed as being more intellectually demanding and methodologically rigorous than the alternatives. The prejudice that basic research entails discovery whilst epidemiology generates statistical associations is often part of the misconception, thriving in isolation from the philosophy of science.

We have no intent to discuss whether basic or epidemiologic (both observational and clinical interventional) research has so far saved more human lives. Future success will likely emerge through close and respectful interaction between these complementary approaches to scientific discovery. Several of our examples above demonstrate that when we as epidemiologists have seized upon a potential discovery and need resolute engagement by basic scientists, we are often hampered by the gap between the two scientific subcultures. We believe that basic scientists—probably more than they realize—also need the assistance of epidemiologists to test hypotheses and to explore the relevance of their discoveries in the population. It is worth mentioning that vaccination against oncogenic viruses—the only good example of basic research contributing dramatically to current opportunities for cancer prevention—was the result of basic scientists and epidemiologists working in concert towards the same goal. Thus, we call for an open discourse about the prioritization of resources and the prevailing disconnect between competitive advantages and resource allocation (Fig. 3).

Currently, the historical dominance of basic research is perpetuated (Fig. 4) and, according to recent data from the National Institutes of Health—the major federal source of biomedical research funding in the US—heavily prioritized with no mentioning of clinical research epidemiology or chronic disease prevention [32]. Data from the Swedish Cancer Society—the main funder of cancer research in our country—is also informative; in 2015, only 12% of the total amount was allocated to clinical, 8% to epidemiologic and 1% to prevention research (Fig. 3). In practice, this distribution of research support implies that large-scale studies in cancer epidemiology are virtually impossible to fund domestically, a situation that has prevailed for decades. Hence, it might be worth discussing if the yield of funders' and donors' investments would increase if we devoted more resources toward research areas—notably epidemiology—where our competitive advantages in the Nordic countries are globally unsurpassed [33], at the expense of some reduction in basic research, where no such advantage exists. A similar open discourse about optimal use of available resources should be encouraged in every country.

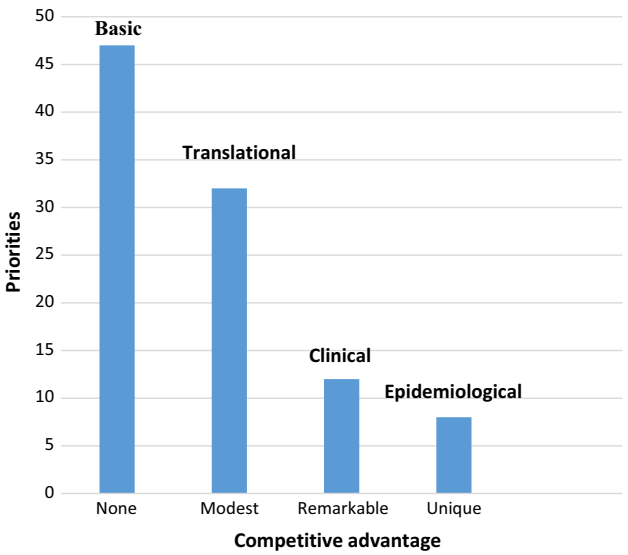

Fig. 3 An approximate illustration of the disconnect between research approaches' (basic, translational, clinical, epidemiological) natural prerequisites for informative studies (competitive advantage compared to most non-Nordic western countries—none, modest, remarkable, unique) and their prioritization in the funding of cancer research in Sweden

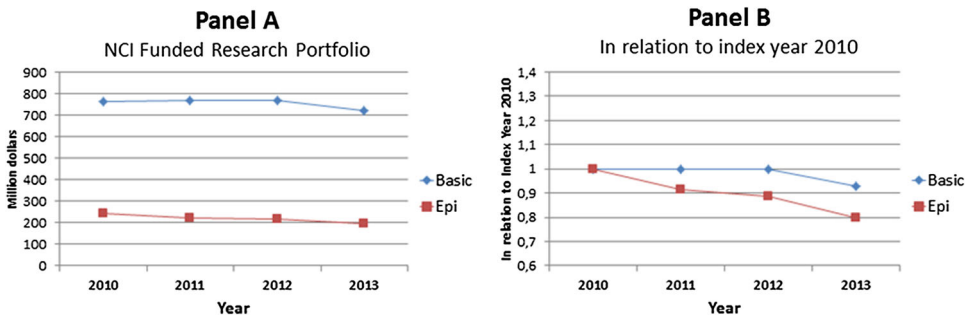

Fig. 4 At the U.S. National Cancer Institute, the funded research portfolio has remained about four–fold higher in basic than in epidemiologic research (Panel A). In relative terms, basic research has been affected by a less than 10% reduction from 2010 to 2013. In contrast, there has been a downward trend in support for epidemiologic research by about 20% over these 4 years (Panel B). No adjustment for inflation

What have pooling studies discovered?

Modern computing capacity has allowed groundbreaking, large or even gigantic pooling projects. Data from most or all informative published studies have been harmonized and analyzed with increasingly sophisticated statistical methods. For a number of established cancer causes—such as tobacco smoking [34] and menopausal hormone treatment [35]—the enormous gain in statistical power has allowed an impressively detailed dissection of various dimensions of the exposure-cancer relationship. From these efforts we have, for example, learned a lot about the (beneficial) effects of quitting smoking or shortening the duration of menopausal hormone treatment [34, 35].

Pooling projects have also provided precise risk estimates for established causes of cancer and allowed us to dismiss exposures suspected to cause certain cancers by providing risk estimates close to unity with narrow confidence intervals. The benefit is, however, more uncertain when weak associations—say, in the range of 1.1–1.4—become statistically significant. Before the era of pooling studies, we usually agreed among epidemiologists that in an observational study, the role of unrecognized bias and confounding could not be ruled out with confidence for such weak associations.

Needless to say, pooling projects are constrained by the exposure data collected to test hypotheses that prevailed when the original studies were launched, often many years or even decades ago. The level of detail in exposure assessment is often suboptimal, particularly in cohort studies aimed to investigate many potential risk factors and multiple outcomes. Moreover, pooling projects often are forced to reduce exposure classifications to the lowest common denominator—that is, to use the crudest exposure categories shared in common across all included studies—to enable data harmonization. Aligning exposure information collected in different ways and in different contexts is challenging and often leads to oversimplification. And possible heterogeneity of the outcome disease may result in confusion rather clarity; our example of divergent incidence patterns for esophageal squamous cell carcinoma in western populations and high-risk Asian populations suggests that there might be two etiologically distinct phenotypes.

But in the zero-sum game of research funding, fewer resources remain for new, original epidemiologic studies to test hypotheses using much more detailed exposure data. Furthermore, a growing number of epidemiologists have hardly ever designed an epidemiologic study and generated the primary data; they thrive on analyzing ongoing cohorts and pooling data collected by others. This clearly limits the breadth of their competence, perhaps reducing their appetite for entering new territory in etiologic research. Without disregarding their important contributions, we ask ourselves if any pooling project has discovered an important new cause of human cancer. And the answer is not obvious to us. Nevertheless, it goes without saying that they attract an increasing share of available resources, human and financial.

The harm of cancer alarm

No consumer of public media can escape exposure to alarming news about suspected causes of cancer. And those who follow the fate of such targets will find that continued research rarely, if ever, transforms them to generally accepted causes of human cancer. Hence, most of this public alarm is just surface appearance and illusion. Salient exceptions exist, such as the tragic effects, discovered 45 years ago in female offspring exposed in utero to diethylstilbestrol [36]. Realization that many causes of cancer likely remain to be revealed also calls for open-mindedness and readiness to follow-up on even weak signals of concern with stringently designed epidemiologic studies.

But the evidence base for a typical cancer alarm has other features. Some emerge from uncritical extrapolation

of animal studies, as was the case when acrylamide was proposed to cause a number of human cancers, a theory not substantiated in subsequent epidemiologic studies [37]. Others emerge from small studies that are difficult to interpret because false positive results tend to outnumber the relatively few true positive results—small study size thus undermines the positive predictive value of a claimed discovery [38]. The most common source of alarm is studies with suboptimal design, non-transparent analysis plans—often with extensive subgroup analyses—and findings uncritically promoted by the investigators. The media attention increases when concerns pertain to large segments of the population; this mechanism explains the countless headlines crying out, for example, that cellular phones cause brain cancer. It took more than a decade until properly designed studies led to a more balanced view on the possibly causal association [39] which brought media alarms to an end.

We argue that the precautionary principle is no excuse for undertaking under-powered studies with a cavalier design. We also believe that cancer alarms may be harmful. False alarms undermine the credibility of our discipline both in the scientific community and among lay people. Most importantly, however, a stream of cancer alarms that gradually disappear over time to become replaced by others may counteract efforts to promote a healthy lifestyle based on solid, well-established evidence; they likely promote a nihilistic sense that everything or nothing matters. Hence, even the giants in the cancer landscape—such as smoking and obesity—may be accommodated less seriously. If so, the paradoxical net effect of a seemingly noble referral to the precautionary principle as an excuse for cancer alarms might be harmful rather than beneficial to public health at large.

We call for a humble approach to our own research findings and a balanced interaction with public media, whereby research findings are preferably interpreted and communicated by individuals with no vested interests. We also need deeper appreciation of the fact that a much larger proportion of our research findings than we would hope turns out to be wrong [40] [41]. The philosophy of science and the continued debate about the many complexities and subjective components of causal inference call for a modesty that would reduce the flow of cancer alarms.

Opportunities

Big Data

Typical for Big Data is that real-time, frequent or continuous, quantitative measurements replace the standard approach in epidemiologic studies of infrequent records of people's memories of past events. Is the concept of Big Data [42] just a new bandwagon, a fashion soon to be replaced by others? We believe that Big Data, similar to other innovations, offers threats and opportunities and that the balance between them is unpredictable. Hence, we argue that the utility of Big Data for our discipline should be thoroughly explored. The attraction, so far with little empirical support, is based on the view that exposure misclassification remains an Achilles heel and a barrier to progress in epidemiologic research.

Consider fundamental characteristics of our lifestyle such as physical activity, diet, occupational hazards, ultraviolet radiation exposure, use of medications such as NSAIDs and antibiotics, etc. All of these factors vary among individuals, change over time and presumably are often different during the etiologically relevant period when malignant transformation of the first cancer cell took place—typically decades ago or even in utero—compared with the time when cancer surfaces clinically.

Notwithstanding the fundamental problem of exposure assessment relevant for the time period when malignant transformation began, an impressive list of causes of human cancer has emerged. Several factors may have contributed to this success. A few prospective studies—such as the British Doctors' and the Nurses' Health Study—have had the resources to repeatedly update exposure data over several decades, thereby enabling them to capture temporal changes. Some features of our lifestyle remain stable over time and are easy to remember, such as smoking. This habit is typically initiated during adolescence and continued steadily until quitting. In some settings, lifestyle may have remained stable over extended periods of time, for example, when diet is constrained by availability of foods or financial resources. And at least in the Nordic countries, self-reported data can sometimes be complemented or validated through linkage to population registers.

But for the majority of suspected causes of cancer—and perhaps the majority of unexplored ones—only new methodologic approaches will reduce misclassification and allow a deeper level of resolution. Currently, Big Data generated chiefly by modern smartphones appears as the most realistic alternative. Hence, novel environmental and lifestyle factors that might cause human cancer would be sought using the agnostic approach combined with replication that has been firmly established by genome-wide association studies. For diseases with a long induction time—such as most malignancies—longitudinal studies with years or decades of continuous exposure assessment and follow-up for outcomes would be needed before informative analyses can be undertaken. Validation studies nested in such longitudinal studies, along with sensitivity analyses, might also improve exposure assessment in contemporary case–control studies.

Innovation

Without claiming any personal innocence, we are concerned about the slow innovation in our discipline. The majority of efforts and resources are devoted to pursue etiologic hypotheses well-known to all of us years or even decades ago, whilst too few investigators row against the flow of ideas that surround us. Admittedly, we have successfully abandoned some suspected causes of cancer and refined the understanding of others. Even if we embrace the substantial role of genetic factors, however, geographic disparities and temporal trends in the incidence of most cancers indicate that many environmental causes with a considerable attributable fraction are awaiting scientific attack. And it seems unlikely to us that the primary suspects we have investigated so extensively already will ultimately explain more than a tiny fraction of the unknown.

Hence, we call for innovation, closer interaction with basic and clinical investigators, and willingness to initiate high-risk, high-yield projects that may take many years to mature. Unfortunately, the current funding climate seems to drive us in the opposite direction, towards low-risk, low-yield and short-term projects. However, recent evidence generated by Big Data approaches might facilitate creativity and innovation. Such research—sometimes called "Social Physics" [43]—can help us understand the flow of ideas, how to maximize the input from brainstorming, create successful teamwork and make collective intelligence exceed that of individuals. In an era when most of us spend our work days in front of a computer screen, embracing the value of social interaction might indeed be crucial for innovation.

Persistence

One salient lesson from our work in the Nobel Assembly is that those ultimately awarded the Nobel Prize made their discovery after many years of feverish struggle, failures, re-considerations and creative teamwork finally leading to a success. But many of them used experimental models amendable to rapid modification, sometimes overnight, with outcomes observable in the short term. In contrast, epidemiologic investigations typically take many years to plan, organize, fund, undertake and analyze. When results finally are in print, few have the energy to start the whole process again.

We believe that a new ethos, inspired by basic scientists, is needed to accelerate the rate of discovery in epidemiology. This ethos may be more urgently needed for case–control studies than for longitudinal studies with resources to collect new data and address novel hypotheses during follow-up. But, as argued above, case–control and cohort studies are complementary, not competing, strategies to discover causes of human disease. And we would like to see case–control studies undertaken sequentially with abandoned, refined, and novel hypotheses addressed as time goes by. At least in the Nordic countries, an infrastructure for an ongoing sequence of case–control studies would be feasible and cost-effective.

The cancer screening conundrum

Screening for early diagnosis of invasive cancer and for detection and removal of precursor lesions is considered fundamental for improved cancer control. Great hopes are indeed invested in the prediction that new imaging techniques, development of biomarkers and genetic testing will not only increase the benefit of screening, but also lay the groundwork for individualized interventions. Meanwhile, cancer screening remains perhaps the most polarized and emotional area in contemporary medicine. Strong vested interests—professional, financial, scientific and political—seem to paralyze any rational approach to resolve the controversy.

Whilst the evidence is compelling that removal of precursor lesions reduce the incidence of large bowel and cervix cancer, mammography screening for breast cancer and prostate-specific antigen (PSA) testing for prostate cancer dominate the stage in the screening controversy. No one questions that medical interventions can be ethically justified only if the benefit is greater than the harm. In mammography screening, however, the controversy escalates due to growing uncertainty about the magnitude of the mortality reduction in the current era of effective, widespread systemic adjuvant therapy [44, 45]. At the same time, the evidence of a substantial, 20–30% overdiagnosis of invasive but non-lethal cancer—in addition to the detection of ductal carcinoma in situ with an unknown natural history but an imperative to often extensive treatment—is accumulating [44, 46]. This evidence obviously shifts the balance between benefit and harm.

Prostate cancer differs in a number of aspects from mammography screening because the few randomized trials are methodologically compromised and their findings inconsistent. In addition, the amount of overdiagnosis of non-lethal cancer is enormous and seemingly uncontroversial. And, to the best of our knowledge, no authoritative body has advocated implementation of population-based screening programs. Nevertheless, opportunistic PSA testing continues in many western countries on an industrial scale. Hence, the controversy over benefits versus harms will predictably continue, as will the need for scrupulous scientific assessment.

We believe that cancer epidemiologists could play a pivotal role in protecting the population from harmful interventions and supporting those that convey a clear net benefit. Our proposal is based on the assumption that any

new randomized trials assessing the efficacy and effectiveness of mammography compared with no screening are unlikely to see the light of day. The last trial was initiated some 30 years ago and it is indeed surprising that numerous authorities keep advocating mammography screening by referring chiefly to randomized trials undertaken when the treatments differed so markedly from those administered today. It is also unlikely that the benefit of PSA testing will be assessed in any new randomized trial.

As a corollary, only observational study designs can expand the evidence base; high-quality ecologic and cohort studies have indeed recently been considered the best designs for investigating overdiagnosis [47]. In the context of cancer screening, case–control studies in particular are extraordinarily challenging to design, often plagued by biases that generate profoundly misleading results. Hence, this is an area in need of committed engagement, methodologic development and critical validation led by cancer epidemiologists. Such an endeavor would be relevant for a growing part of the global population, and most likely for future screening tools and for cancer sites other than those that are currently under scrutiny.

Conclusions

In this essay, we have briefly outlined a few of the intriguing enigmas, concerning priorities and unexplored opportunities that we jointly agreed might be relevant for the progress of our discipline. But as scholars, we are driven by doubt and curiosity, not by conviction. Hence, nothing is written in stone and we would rather welcome an open, critical debate—louder than we have heard during our life in science—about future directions. We disagree with the common perception that all of the predominant risk factors for cancer have been identified and that only factors of modest or incremental importance remain to be discovered. For example, the unexplained, more than 50-fold geographic variation in the incidence of esophageal squamous cell cancer as well as nasopharyngeal carcinoma [48], an approximately tenfold disparity in testicular cancer around the Baltic and a 250% increase in colorectal cancer in Norway make such pessimistic predictions unlikely. Instead, we remain fascinated by the fact that important discoveries remain unpredictable and never occur as results of political decision, strategic prioritization, short-term fashion or walking in others' footsteps.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Le Fanu J. The rise and fall of modern medicine. New York: Carroll & Graf; 2000.
2. Adami HO. Epidemiology and the elusive Nobel Prize. Epidemiology. 2009;20:635–7.
3. Edgren G, Liang L, Adami HO, Chang ET. Enigmatic sex disparities in cancer incidence. Eur J Epidemiol. 2012;27(3):187–96. doi:10.1007/s10654-011-9647-5.
4. Abnet C, Nyren O, Adami HO. Esophageal cancer. In: Adami HO, Hunter D, Lagiou P, Mucci LA, editors. Textbook of cancer epidemiology. 3rd ed. New York: Oxford University Press; 2017.
5. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer incidence in five continents: inclusion criteria, highlights from volume X and the global status of cancer registration. Int J Cancer. 2015;137(9):2060–71. doi:10.1002/ijc.29670.
6. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108. doi:10.3322/caac.21262.
7. He Y, Wu Y, Song G, Li Y, Liang D, Jin J, et al. Incidence and mortality rate of esophageal cancer has decreased during past 40 years in Hebei Province, China. Chin J Cancer Res. 2015;27(6):562–71. doi:10.3978/j.issn.1000-9604.2015.10.06.
8. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32. doi:10.3322/caac.21338.
9. Abnet CC, Kamangar F, Islami F, Nasrollahzadeh D, Brennan P, Aghcheli K, et al. Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomark Prev. 2008;17(11):3062–8. doi:10.1158/1055-9965.epi-08-0558.
10. Chen X, Winckler B, Lu M, Cheng H, Yuan Z, Yang Y, et al. Oral microbiota and risk for esophageal squamous cell carcinoma in a high-risk area of China. PLoS ONE. 2015;10(12):e0143603. doi:10.1371/journal.pone.0143603.
11. Ye W, Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, et al. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. J Natl Natl Cancer Inst. 2004;96(5):388–96.
12. Nasrollahzadeh D, Malekzadeh R, Ploner A, Shakeri R, Sotoudeh M, Fahimi S, et al. Variations of gastric corpus microbiota are associated with early esophageal squamous cell carcinoma and squamous dysplasia. Sci Rep. 2015;5:8820. doi:10.1038/srep08820.
13. Nasrollahzadeh D, Ye W, Shakeri R, Sotoudeh M, Merat S, Kamangar F, et al. Contact with ruminants is associated with esophageal squamous cell carcinoma risk. Int J Cancer. 2015;136(6):1468–74. doi:10.1002/ijc.29109.
14. Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. Gut. 2013;62(10):1406–14. doi:10.1136/gutjnl-2012-302412.
15. Ghasemi-Kebria F, Roshandel G, Semnani S, Shakeri R, Khoshnia M, Naeimi-Tabiei M, et al. Marked increase in the incidence rate of esophageal adenocarcinoma in a high-risk area for esophageal cancer. Arch Iran Med. 2013;16(6):320–3.
16. Fan YJ, Song X, Li JL, Li XM, Liu B, Wang R, et al. Esophageal and gastric cardia cancers on 4238 Chinese patients residing in

municipal and rural regions: a histopathological comparison during 24-year period. World J Surg. 2008;32(9):1980–8. doi:10.1007/s00268-008-9674-x.
17. Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol. 2015;45(9):884–91. doi:10.1093/jjco/hyv088.
18. Hansson LE, Bergstrom R, Sparen P, Adami HO. The decline in the incidence of stomach cancer in Sweden 1960–1984: a birth cohort phenomenon. Int J Cancer. 1991;47(4):499–503.
19. Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. JAMA. 2010;303(17):1723–8. doi:10.1001/jama.2010.496.
20. Song H, Held M, Sandin S, Rautelin H, Eliasson M, Soderberg S, et al. Increase in the prevalence of atrophic gastritis among adults age 35 to 44 years old in Northern Sweden between 1990 and 2009. Clin Gastrol Hepatol. 2015;13(9):1592–600. doi:10.1016/j.cgh.2015.04.001.
21. Hansson LE, Nyren O, Hsing AW, Bergstrom R, Josefsson S, Chow WH, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. N Engl J Med. 1996;335(4):242–9. doi:10.1056/nejm199607253350404.
22. Giovanucci E, Keum N, Wu K, Hunter D. Colorectal cancer. In: Adami HO, Hunter D, Lagiou P, Mucci LA, editors. Textbook of cancer epidemiology. 3rd ed. New York: Oxford University Press; 2017.
23. Graff R, Möller S, Passarelli M, Witte J, Skytthe A, Adami H, et al. The familial risk and heritability of colorectal cancer in the Nordic Twin Study of Cancer (NorTwinCan) (submitted).
24. http://www-dep.iarc.fr/NORDCAN/english/frame.asp. Database on the Internet. Accessed 28 June 2016.
25. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al. Familial risk and heritability of cancer among twins in nordic countries. JAMA. 2016;315(1):68–76. doi:10.1001/jama.2015.17703.
26. Adami HO, Bergstrom R, Mohner M, Zatonski W, Storm H, Ekbom A, et al. Testicular cancer in nine northern European countries. Int J Cancer. 1994;59(1):33–8.
27. Bergstrom R, Adami HO, Mohner M, Zatonski W, Storm H, Ekbom A, et al. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. J Natl Cancer Inst. 1996;88(11):727–33.
28. Frisch M, Glimelius B, van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med. 1997;337(19):1350–8. doi:10.1056/nejm199711063371904.
29. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825–31. doi:10.1056/nejm199903183401101.
30. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. Lancet. 1992;340(8826):1015–8.
31. Ye W, Chang E, Liu Z, Huang G, Zeng Y, Zeng Y, et al. Development of population-based research methods in China (submitted).
32. Lowy DR, Collins FS. Aiming high—changing the trajectory for cancer. N Engl J Med. 2016;374(20):1901–4. doi:10.1056/NEJMp1600894.
33. Adami H-O. A paradise for epidemiologists? Lancet. 1996;347(9001):588–9.
34. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519. doi:10.1136/bmj.38142.554479.AE.
35. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet. 1997;350(9084):1047–59.
36. Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med. 2011;365(14):1304–14. doi:10.1056/NEJMoa1013961.
37. Mucci LA, Adami HO. The plight of the potato: is dietary acrylamide a risk factor for human cancer? J Natl Cancer Inst. 2009;101(9):618–21. doi:10.1093/jnci/djp080.
38. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365–76. doi:10.1038/nrn3475.
39. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, part 2: Radiofrequency electromagnetic fields. Lyon: The International Agency for Research on Cancer; 2013.
40. Ioannidis JP. Why most published research findings are false. PLoS Med. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124.
41. Boffetta P, McLaughlin JK, La Vecchia C, Tarone RE, Lipworth L, Blot WJ. False-positive results in cancer epidemiology: a plea for epistemological modesty. J Natl Cancer Inst. 2008;100(14):988–95. doi:10.1093/jnci/djn191.
42. Mayer-Schönberger V, Cukier K. Big Data: a revolution that will transform how we live, work, and think. London: John Murray; 2014.
43. Pentland S. Social physics: how good ideas spread—the lessons from a new science. New York, NY: Penguin Press; 2014.
44. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med. 2016;375(15):1438–47. doi:10.1056/NEJMoa1600249.
45. Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. N Engl J Med. 2010;363(13):1203–10. doi:10.1056/NEJMoa1000727.
46. Kalager M, Adami HO, Bretthauer M, Tamimi RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. Ann Int Med. 2012;156(7):491–9. doi:10.7326/0003-4819-156-7-201204030-00005.
47. Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. BMJ. 2015;. doi:10.1136/bmj.g7773.
48. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomark Prev. 2006;15(10):1765–77. doi:10.1158/1055-9965.epi-06-0353.