Modern approaches to cancer prevention: Universal or personal?

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A R T I C L E   I N F O

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There is a push on nowadays to adopt a personalized approach to medicine and much of the enthusiasm comes from within the cancer community. The first of two dominant themes is that we could better choose a patient's treatment by having a comprehensive knowledge of the genetic makeup of his or her tumor. DNA sequencing may identify a 'targetable' gene or a pathway of proteins that will render the cancer vulnerable (the relevant drugs are called 'biologics'). The other dominant theme is personalizing prevention. That is, because we do not all share the same inherent risk for cancer it would be wise to identify and target those at high risk for special attention. This goes beyond one's sex and the retention of susceptible organs (e.g., ovaries or uterus). Factors such as smoking, prior therapeutic radiation, family history and sexual exposure to papillomavirus are all helpful to identify high-risk individuals, but what we are really talking about are the risk factors that we carry about unawares—fortunately for us we can test for in the laboratory or in the clinic.

In order for a preventive program to work there has to be a preventive agent on offer. If there is no means of prevention there is no expectation of benefit. If vitamins prevented cancer we could heartily recommend them to everybody. No need for personalized medicine. A healthy lifestyle is good for all and so we can afford to be generous with our advice. But few interventions come without cost and many have side effects. The principal arguments against offering universal (as opposed to personalized) prevention are cost and side effects. For imaging it is mostly about costs; for chemoprevention it is mostly about side effects.

Population stratification for screening purposes

The premise underlying the personalized approach is that we will prevent more cancers for the same money if we categorize people and ration wisely. But if mammography works why not offer it to everybody? The first division of the population into risk strata was based on age alone; in some places the age cutoff for mammography was forty, elsewhere fifty. After 40 years we are not sure if this simple policy is effective [1–3] and there is a move afoot to replace it with something less simplistic. To some extent, the case for a personalized approach to breast screening may be a reaction to what is perceived as an unsatisfactory outcome with conventional screening. Some (like the Swiss) argue, based on recent results from the Canadian Breast Cancer Screening Study, that mammography should be scrapped [3]. Vehement supporters of mammography claim the Canadian study was fatally flawed and that we should continue to screen as always [4–6]. But others take a 'middle ground'. They say that mammography does not work as well as we would like when offered to all women and so we should tailor screening according to level of risk. This argument is not based on logic or evidence, but is an opinion that once heard, some people repeat when they wish to sound thoughtful. If mammography is good for high-risk women but not for low-risk women, then surely this would be because of false positives, high costs, side effects and marginal benefits—but these are not the central issues—it is the lack of an observed mortality reduction associated with early detection that belies the limits of mammography. Mammography might work in high-risk women but not in low-risk women if the biologic characteristics of the cancers were different and not merely the prevalence. For example, small breast cancers in BRCA1 carriers are more aggressive than average cancers [7] and over–diagnosis is less of a problem [8], but there is also a high mortality associated with small node-negative hereditary cancers [7] and there is little correlation between tumor size and survival for small BRCA1-positive cancers [7,9]. MRI has now been adopted widely for screening of mutation carriers [10,11]. Studies to date that support the use of MRI in BRCA1 carriers are based on sensitivity [12–14] and not on mortality and we should not take a mortality benefit for granted. One study from Norway found that of 68 women with a BRCA1 mutation and breast cancer detected through MRI, ten succumbed to their disease, despite being diagnosed early [15].
Personal predictive genotypes

It is possible to prevent breast cancer in BRCA1 carriers through prophylactic mastectomy [16], oophorectomy [17] and tamoxifen [18]. But BRCA1 variants are rare and only one in 500 Canadian women are at risk because of one. There are many other genetic variants that increase one’s risk of cancer. They may be in a highly penetrant gene (e.g. BRCA2), in a moderately penetrant gene (such as CHEK2) or in a low penetrant gene (single nucleotide polymorphism). It has been supposed for a decade now that common, low penetrant genetic variants may have greater population attributable risks than genes like BRCA1 [19]. There are thousands of SNPs scattered throughout the genome – some are located in genes, some are in nearby gene regulatory regions and some are in places where they have no clear impact on gene expression or function. Through a series of rigorous and comprehensive genome-wide association studies (GWAS) involving thousands of SNPs, thousands of cases and controls (and hundreds of authors), 100 or so SNPs have been shown to be reliable predictors of breast cancer risk [20–22].

The prevalence of the high risk alleles in general fall between 1% and 30% and the relative risks fall between 1.1 and 1.4. For a single SNP, the population risk attributable is below 3%. However, assuming a multiplicative model, a panel of ten or more SNPs might be used to assign women to a high (or low) risk. For example, if each of ten SNPs has a prevalence of 0.10, a relative risk of 1.2 for the risk allele and a relative risk of 0.95 for the low risk allele (compared to untested women), then a woman with five of ten possible risk alleles would have a composite risk ratio of about two. But only two in 1000 women in the population would have a risk of two-fold or higher.

The translational promise from all of this work on SNPs is that we can use personal predictive genotyping to tailor screening (lifestyle is not on issue, one must eat well and exercise frequently regardless of one’s genotype. No-one is serious enough to propose preventive mastectomy on the basis of a few SNPs, and healthy women at much higher levels of risk rarely take tamoxifen). In the case of SNPs, screening is the best medicine. Hence it is proposed that women at high a priori risk should either qualify for MRI screening or go for mammograms early. In Ontario, MRI is expensive and a 25% lifetime risk is the current requirement. An alternate proposal is that women at high risk based on a predictive genetic test result be offered mammography from age 40, not 50. Consider a scenario wherein the top one percentile of the population experience a twofold increase in risk. If ten percent of the women in Canada opt to pay for the test (or have it paid for them) then one in 1000 Canadian women will be found to be at high risk. Suppose, for them, screening begins at age 40 instead of age 50. The cumulative incidence of breast cancer from age 40 to 50 is about 1% in Canada, and doubling it will raise it to 2%. If screening is associated with a 30% reduction in mortality and if the baseline case fatality of breast cancer is 30%, then we can expect to save the lives of two women in a million as a result of the new program (and 40,000 other Canadian women will die of breast cancer nevertheless). It is perhaps not unexpected, that given the enormous cost of the GWAS enterprise, in terms of hard cash and intellectual currency, that the proponents of genetic risk stratification should support the SNP paradigm despite having neither evidence nor promise.

Personalized medicine in the clinic

For some risk factors, such as family history, age of menarche, parity and breastfeeding, exposure status will be known by almost 100% of women at the time of the clinic visit and it requires little or no investment to retrieve the relevant information. Other risk factors, such as mammographic density and atypical hyperplasia require an investment in time, cost and perhaps morbidity. Very few women know their mammographic density and most women with atypical hyperplasia are unaware of it. In order to ascertain one’s genetic risk stratum, one needs to undergo a genetic test. The test result will need to be interpreted and explained. Perhaps a genetic counselor should be involved. The underlying premise of genetic risk stratification is that all women in the population are candidates for the upfront test; women are not pre-selected based on disease status or on family history. If genetic counseling is indicated, then we are committed to offering counseling to all. The process will be further complicated if the patient also has a family history, because it will be necessary for a professional to sort out both the family history and the genotype information. Should someone high up in the health care system decide that it is acceptable to withhold screening to women based on a low personal risk then someone else will have to explain this to the patient, who may or may not welcome the news. If the test is offered to all women, is it likely to be included as part of a national health care system or to be reimbursed by a third-party payer? Perhaps the woman herself will pay for the test. How many will pay? I guess the number will be below ten percent, perhaps as low as one percent. If a private company can market a genetic test to 10% of the general population then it would be financially successful, but if a public health unit enrolled only 10% of the target population in a screening program then it would probably be considered a failure. If the goal of a cancer prevention initiative is to reduce the incidence of cancer in the population then a reduction in incidence should be the criterion under which the program is evaluated. Predictive genetic testing can, in some cases, generate odds ratios that are clinically meaningful, but even a cursory analysis of the public health implications of genetic risk stratification compels the conclusion that this will have little or no impact on cancer rates. The promise of personalized medicine was to identify a simple test that could categorize the majority of potential cases within a subgroup of the population. If they gave us a risk classifier that would correctly predict 90% of breast cancers in ten percent of the population, the promise would be fulfilled. But that would entail an odds ratio of 81 for a risk factor with a prevalence of 10%. Instead we are given an odds ratio of two with a prevalence of 1%.

Potential for reducing cancer incidence in BRCA mutation carriers

Arguably one of the most effective strategies available at present for preventing cancer is to offer preventive oophorectomy to women with a BRCA1 or BRCA2 mutation [17]. 13% of women with ovarian cancer have a mutation [23] and these are potentially preventable if the mutation could be identified prior to diagnosis. This would require a genetic testing policy that would include 100% of carriers as eligible for testing and a referral mechanism that would identify them and refer them for testing. Furthermore, the patients would wish to have genetic testing and in the event of a positive test, agree to oophorectomy. In a recent study from Ontario, we have shown that 3.6% of women with ovarian cancer were eligible for genetic testing prior to the test [24]. This implies that if all eligible women were identified and referred for testing and were subsequently tested and accepted oophorectomy, and if oophorectomy were 100% effective, then we could prevent 3.6% of cases (36 cases a year in Ontario). Realistically, suppose that only 20% of eligible women were recognized as such and offered testing, of whom 80% accepted, 75% had an oophorectomy and that oophorectomy was 80% effective, then the fraction of cancers prevented drops to one in 300, or four cases annually in Ontario (far less than one percent). The reality of tamoxifen chemoprevention is even less impressive. Assume that 5% of women with breast cancer have a
BRCA1 or BRCA2 mutation and that one in ten women with a mutation is aware of her mutation status prior to diagnosis. Currently about 5% of healthy women with a BRCA mutation take tamoxifen [25]. Suppose that tamoxifen reduces the incidence of breast cancer in BRCA carriers by 50%. On a population level, the program would prevent one in 8000 cases in Ontario, or roughly one case of breast cancer per year.

**Other high risk genes**

BRCA1 is a high-risk gene and the clinical benefit from testing is largely attributable to oophorectomy. Oophorectomy is common among carriers and prevents ovarian cancer, breast cancer and death from breast cancer [17]. Mastectomy is also effective [16] but the uptake is far less [25].

For genes such as CHEK2, ovarian cancer does not feature and oophorectomy is not proposed; prevention relies on tamoxifen and screening [26]. CHEK2 testing is not yet widespread and there is no evidence that testing for CHEK2 will have an impact on cancer risk. Several companies offer genetic panel testing for a larger number of genes associated with an increased breast cancer risk, including CHEK2, but testing for these is currently limited to a few women and the clinical utility has not been shown. In one study reported to date, 198 women who had qualified for testing for BRCA1 and BRCA2 were offered extended panel testing for 42 cancer related genes, including BRCA1, BRCA2 and 40 other genes [27]. Of these, 57 carried a BRCA1 or BRCA2 mutation and six women carried a mutation in another breast cancer gene (ATM, BLM, CDH1, NBN and SLX4). These six women were advised to consider annual MRIs because of an (estimated) doubling of cancer risk (even though several already had breast cancer). There was no discussion of tamoxifen or preventive mastectomy. The authors conclude that “these results suggest that multiple-gene testing may benefit appropriately selected patients.” I have no idea how they reached this conclusion.

**Should we adopt a personalized approach?**

There is insufficient data to support a publicly funded health initiative based on personal genotyping with SNPs. The odds ratios are far too small to be useful, even in combination, and yet there is the potential to greatly increase the quantity of genetics and counseling delivered. The costs of the counseling, genotyping and additional imaging cannot be justified based on the expectation of lives saved or cancers prevented. To a large extent, the current clinical position—which is adopted by the majority in the clinical cancer genetics community, reflects an attempt to justify the past expense of the GWAS studies and to translate these findings into clinical care. The GWAS studies were driven by innovation in technology and the widespread public attention garnered by the human genome sequencing initiative. The development of a comprehensive map of human polymorphic variation and the release of chip-based technologies made it possible to evaluate many loci simultaneously and it was expected that these studies would reveal the inner nature of cancer susceptibility. It is too early to say if the genes identified through these studies will eventually lead to a sufficient number of useful drugs to justify the expense.

Genetic testing for the two high-risk genes BRCA1 and BRCA2 can clearly benefit individual patients. The majority of benefits are attributable to oophorectomy and mastectomy, and the benefits of tamoxifen or MRI screening have yet to be demonstrated. Nevertheless in terms of the entire population, unless testing becomes universal, under current protocols we cannot expect to experience a decline in breast or ovarian cancer risk that exceeds one percent of the baseline incidence after the introduction of a genetic test for BRCA1 and BRCA2. Exceptions may be in countries with high prevalence of founder mutations such as Israel [28] and the Bahamas [29]. A second wave of technological innovation (next generation sequencing) and in the reversal of the courts in the Myriad patent position led to a rapid expansion of the number of providers of genetic testing and in the spirit of competition has led to a transition from two-gene testing (BRCA1 and BRCA2) to navigational panel testing. Mutations in these supplemented genes are rare. For most of these, the risk estimates for breast cancer risk are low (or imprecise) and mastectomies will be uncommon. For most of these, the risk of ovarian cancer is too low to prompt oophorectomy. Given the rarity of mutations and the reliance on screening and tamoxifen for women with mutations in these genes, the addition of multiple genes to the basic BRCA1 and BRCA2 test through comprehensive panels is not likely to prevent very many breast cancers. Individual patients may benefit but national cancer incidence rates will be unperturbed.

**Conflict of interest**

The author declares that he has no conflict of interest.

**References**


