Welcome to the next edition of P5 Protocols. For those listening via iTunes or SoundCloud but not yet subscribed, please go to www.p5protocols.com and in the upper right corner click on Contact Us and sign up for our newsletter, P5 Insights, as well as a link to this podcast, to be directly emailed to you.

This week, we have two discussions:

- The first is about ***the concept*** of how a handful of fairly large $$$ checks could have a profound impact on learning about disease and how they could be better treated. Think about the power of incremental learning and compounding, or the application of finance and behavioral psychology to the practice of medicine

- The second area I want to tackle is how do the common ways of medicine become, well, the common ways, otherwise known as standard of care. I have my theories and some of them are based on my overly simplistic patient perspective, but they have implications about what people think and are willing to do. Part of this is the way human beings react to news, which of course is rapidly evolving like everything else. We are at the precipice of radical changes in healthcare, but I'm betting they are not the ones you think. It's just human nature to group around one view while the ultimate "truth" shows up in a different place or direction.

PART I

On to the first topic:

So here is my bet and call it a challenge if you will: I would bet that for $50 or $100 million or maybe even less - about the cost of a good painting for a few successful art collecting hedge fund managers, or a drop in the bucket for a few large foundations, or the first step in the development of a major drug that may benefit society in ten years at $300,000 to $800,000 per patient per year - I'm betting that with five years of incremental non-invasive trials, we could prove with overwhelming data and insight that various combinations of integrative oncology, including nutrition, detoxification, hormone balancing, ketogenic diet, and other bodily support, can by all statistical measurements outperform just about every standard of care currently on the market, including where immunotherapy will be in five years; and as a bonus, we would help many lives along the way. And this would apply to most diseases. I would further "bet" (a term I hate to use when human lives are on the line, but something has to incite others to action) that it doesn't have to replace "standard of care" completely - to the contrary in fact.

Another name for functional or integrative medicine is complementary medicine. What I believe is lost is that ALL OF MEDICINE should be complementary. All options should be considered and where appropriate used, and if a doctor does not know nutrition or forms of meditation or movement, then that doctor has an obligation to find high performers in those respective fields and associate with them and refer out their patients - especially when the options are low-risk.

In other words, if alternatives help or even are best for a person, but standard of care or parts of standard of care could be helpful, then do them both, or vice-versa.

No one should care what the “standard” is and which component is complementary. So, add in machine learning and some intelligent algorithms so that we become collective learning systems or machines, then by the time 10 years has passed, we could have dramatic improvements in outcomes, just in time for today’s research to hit the market. Wait another 5 to 10 years and we may have nanobots fixing our cells and DNA. But I am focused on saving those living today dealing with today’s medical problems in today’s payer environment. So, when I apply compounding as seen through an investor’s eye

- At a 5% per year improvement in outcomes, after ten years, we have a 63% improvment in overall outcomes
- At 7.5% per year, 106%
- At 10% per year, 259%
- At 12.5% per year, 325% improvement

Further, I am likely using low figures in terms of gain, and when I refer to gain, I am referring to both healthspan or quality of life as well as lifespan. Once we start breaking into 25 to 50% improvements, I would put high odds on hockey stick shaped or exponential returns.

So, lots of little things in complementary fashion. We can study the Paracelsus Institute and other institutions that have better outcomes. I’m always amazed when doctors will stick a patient in a radical Hail Mary clinical trial but not, by example, a ketogenic diet… It’s the compounding of small improvements that matter. But someone has to lead the way. That remains the essence of our focus on a foundation that we are attempting to put together - though that too must be in collaboration with others!

So who is willing to write that check? Not pharmaceutical companies, because they can’t patent a series of services. Or could they? To get in the good graces of Congress, do they need to? Do the founders of the big technology companies need to do this to give back and deflect criticism that can lead to their breakup?

Of note, it is a shame that “no one” has yet in a big meaningful way written that big check to kick it off. It should be in a system that writes checks to verify various claims, use the computer platform to analyze outcomes and further back trials to prove out certain protocols and then start mixing and matching, starting with less invasive modalities standardized so as to bear out repetition. One example of a company with a protocol worth further study, but in which we recently passed on investing due to its business model, is a clinic business with a very interesting cocktail of four generic drugs that cost almost nothing that in combination appear to have a profoundly positive effect on stopping cancer - all kinds of cancer! The company’s name is Care Oncology and while they are based in London, they have an outlet here under the leadership of Travis Christofferson, past podcast guest and author of Tripping Over The Truth.

Though the sample size is only 99 patients in their glioblastoma study, it so blows away standard of care data as to be statistically significant. Does anyone know a cancer patient out there taking Metformin, a 60 plus year old safe drug?

But instead, my current belief, which I hold the right to change at any time and PRAY that I do, is that the world is still hit driven. Meaning pharma, big drug, big win driven. For a patient to win, and the focus MUST be on the PATIENT, it requires removing stressors, they emotional or physical as well as lots of little beneficial things that create lots of little wins that build momentum or what I will call positive inertia toward a healing and ultimately healthy state. With current medicine as practiced in most places, I firmly believe that there is near zero focus on stopping what is harming the patient and only on a limited set of tools that they hope but do not know can fix the patient. I liken it to feeding the enemy while simultaneously trying to kill it. Doesn't make a lot of sense to me.

So how did we get here? I could write 10 or 20 behavioral psychology related articles on this with the concept of antibiotics led us to believe in monotherapeutics, the role of doctors going to the same medical institutions and attending the same conferences, as well as this need for standardization that applies in all Western scientific endeavors, oft failingly so… As a doctor and former advisor to our firm said - and I paraphrase: if you want to get a device or drug into the mainstream and assuming safety and FDA issues aside, in each field, you need to enroll the top 1 or 2 doctors by reputation and get then to use that device or drug and then speak about it at the main conference. At that point, most will follow them. It's that simple, but remember not to confuse simple with easy.

Part II

At P5 Health Ventures, we currently are investing in the next generation of healthcare delivery, because not only is there real benefit to be had, but, as mentioned, we see healthcare about to change much more quickly than people think - both in the delivery and the type of care. This will happen faster than even JP Morgan, Amazon and Berkshire Hathaway can say: Warren Buffett, or all joking aside, faster than three behemoths can collectively act. In normal human behavior, there is a desire to look backward, particularly to the recent past. Behavioral psychologists have a great name for it, recency bias.

In the past decade or two, the new ways of medicine have been relatively slow to proliferate, so some would say it won't happen for a long time; but, I think we are hitting critical mass and social media as well as new ways of measuring efficacy and financial returns will send these new ways flying in popularity and use. Not to beat a dead horse, but does anyone have even a wisdom of crowds type guesstimate of, post Angelina Jolie's statement, how many women had their breasts and other organs brutally cut out because it became established fact that the BRCA genes cause cancer? Did you see the January 11, 2018 Lancet study that found no discernible difference in outcomes between BRCA positive and negative? For those of you

listening, at the end of the transcript, I pasted in the entire results from the Lancet study so you can look at the statistics for yourself.

This brings me to the second half of this podcast about why I think medicine will change faster than we think. I am entitling this section:

The Power of Human Behavior and the Impact of Star Power and Social Media

The other night, I was cleaning up my PDF viewer. Luckily, I stumbled on a still opened article with my markings all over it. It was from a November 17, 2017 newsletter from Epsilon Theory, written by Ben Hunt, my good friend and local (when he is not traveling) savant. You can find it at www.epsilontheory.com. Heads of governments and central banks and big hedge funds listen to him and read his work on applying the common knowledge subset of game theory to economics and financial markets.

If you ever meet Ben, ask him to do his Ben Bernanke impersonation. I'm sure he will verbatim remember that skit from our Iridian holiday party in December 2010. Ben, Hunt that is, is probably the leading expert in the world in the common knowledge subset of game theory. It is based on predicting behavior not based on what you know, but rather what you think everyone else thinks or knows to be true. I hope I said that right. One of the recurring themes in our newsletter is and will be the application of the common knowledge subset of game theory to predicting the practice of medicine, and thus informing our investment direction and choices in whom we invest.

This piece below was supposed to be a short snip (no pun on genetics intended) from that November 17th edition of Epsilon Theory, but I failed to cut out much. It delves into how common knowledge comes to be, well, common knowledge. With some very minor artistic license to hide names and shorten where I can, I quote the following:

> … The thing about the Common Knowledge Game... is that once you start looking for it, you see it everywhere, not just in our investment lives, but also in our social and political lives. The public unmasking of [several celebrities] as serial rapists is an archetypical play of the Common Knowledge Game, and recognizing its dynamics should open everyone's eyes to how other high and mighty people and ideas can take a fall….
>
> The core dynamic of the CK Game is this: how does private knowledge become – not public knowledge – but common knowledge? Common knowledge is something that we all believe everyone else believes. Common knowledge is usually also public knowledge, but it doesn't have to be. It may still be private information, locked inside our own heads. But so long as we believe that everyone else believes this trapped piece of private information, that's enough for it to become common knowledge.

> The reason this dynamic – the transformation of private knowledge into common knowledge – is so important is that the social behavior of individuals does not change on the basis of private knowledge, no matter how pervasive it might be. Even if everyone in the world believes a certain piece of private information, no one will alter their behavior. Behavior changes ONLY when we believe that everyone else believes the information. THAT'S what changes behavior. And when that transition to common knowledge happens, behavior changes fast.

Think about the shoe bomber - everyone likely wanted more protection at the airports and thus on the planes and therefore did not complain when one inept terrorist got a C4 laden shoe on a plane and caused endless billions of passengers to take off their shoes when going through security. It should have happened long before but this put it into the limelight enough for all to believe it is appropriate. I believe this is what is building in integrative medicine. At dinner the other night, a friend said; when you are diagnosed with cancer, the first thing you do is go 100% organic and clean up your diet. Now that was a breath of fresh air, but I had to inform her that virtually every major medical center in America does not teach nor preach that. Now back to Ben and Epsilon Theory:

> The classic example of this is the fable of The Emperor's New Clothes. Everyone in the teeming crowd possesses the same private information – the Emperor is walking around as naked as a jaybird. But no one's behavior changes just because the private information is ubiquitous. Nor would behavior change just because a couple of people whisper their doubts to each other, creating pockets of public knowledge that the Emperor is naked. No, the only thing that changes behavior is when the little girl (what game theory would call a Missionary) announces the Emperor's nudity loudly enough so that the entire crowd believes that everyone else in the crowd heard the news. That's when behavior changes.
>
> And so it was with these celebrity rapists.
>
> Apparently it was no great secret that [they were] serial rapists. Apparently everyone in Hollywood was familiar with the stories. It was ubiquitous private knowledge,and pretty darn ubiquitous public knowledge. I mean, if you're making jokes about it on 30 Rock, it's not exactly a state secret.
>
> But there was never a Missionary. There was never anyone willing to shout the information so loudly and so publicly that it became common knowledge. That's what [one woman and eventually others] did, and that's the power of Twitter and modern celebrity – to establish Missionaries and create common knowledge.
>
> Once that common knowledge was created, once all the private holders of all of one man's dirty secrets believed that everyone else believed that he was a serial rapist, then

everyone's behavior changed on a dime. His publicists and lawyers and partners and colleagues and board of directors and wife were shocked … shocked! … to hear of his behavior, and certainly would no longer be representing him or working with him or associating with him ever again, even though NOTHING had changed in the information they already possessed. Ditto with his [and this applies to many other rapists] other victims. Their behavior changed, as well. That's not a knock or a slam on them. In the absence of common knowledge, staying quiet whether you're an abettor or a victim – is the rational thing to do. In fact, this is what [these rapists] and [their] abettors count on, that their threats and shaming and bribes will set up a Hobson's choice for victims. [more on that another day] Sure you can go public, but no one will believe you and then we will ruin you. So yeah, go ahead. It's your choice. Of course no one goes public, because ...Only a victim with Missionary power (and that's a really rare thing) has the option to not just go public with the story – because simply going public is not enough to change behavior – but to create common knowledge with the story.

What are the broader lessons to take from all this? I've got two.

First, there's enormous economic, political, and social power in being a Missionary and social media has completely transformed the Missionary creation process just over the past few years. This is why it matters how many Facebook followers you have and how many RTs you get on Twitter. This is why Donald Trump adopted social media so early and used it so prolifically. Twitter in particular is a Common Knowledge platform of great power. Having lots of followers isn't "monetizable" in the sense of traditional marketing. But that doesn't mean it's not incredibly valuable. Put differently, *celebrity* in and of itself has never been a greater source of political power than it is today. Why? Because of the Common Knowledge Game.

Second, there's a lot of ubiquitous private information about powerful people and powerful ideas trapped in the crowd today, just waiting for a Missionary to release it as common knowledge. The more powerful the person or the idea to be brought low, the bigger the Missionary (and platform) required. But nothing's too big, and once the common knowledge is created, behavior changes fast.

Wow, that was a mouthful. Again, I started out thinking I would pull a paragraph or two, but this is powerful stuff. I am going to have Ben on this podcast soon enough. At Epsilon Theory, an investor newsletter, to be found at www.epsilontheory.com, where you can subscribe for free!, Ben's pick for moving from private to common knowledge is inflation. My pick for the big idea that gets taken down is "standard of care." I think each disease will happen a few at a time until the dam bursts. We all know standard of care for most diseases doesn't work well. We all know that eating better makes a profound difference; that exercise works to help cure or recover from disease, but it remains private knowledge, only practiced by an educated and disciplined few.

For now...

But we're only a few big Missionary statements away - economics demand it

Thank you for joining us here at P5 Health Ventures. Again, if you are not registered, please do not hesitate to do so at www.p5protocols.com and click on Contact Us in the upper right corner where you will find a box to add your email or send us an email at protocols@p5hv.com. Have a great Super Bowl and make sure you don't overeat! Until next time… Thank you

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Germline *BRCA* mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study

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Summary

Background

Retrospective studies provide conflicting interpretations of the effect of inherited genetic factors on the prognosis of patients with breast cancer. The primary aim of this study was to determine the effect of a germline *BRCA1* or *BRCA2* mutation on breast cancer outcomes in patients with young-onset breast cancer.

Methods

We did a prospective cohort study of female patients recruited from 127 hospitals in the UK aged 40 years or younger at first diagnosis (by histological confirmation) of invasive breast cancer. Patients with a previous invasive malignancy (except non-melanomatous skin cancer) were excluded. Patients were identified within 12 months of initial diagnosis. *BRCA1* and *BRCA2* mutations were identified using blood DNA collected at recruitment. Clinicopathological

data, and data regarding treatment and long-term outcomes, including date and site of disease recurrence, were collected from routine medical records at 6 months, 12 months, and then annually until death or loss to follow-up. The primary outcome was overall survival for all *BRCA1* or *BRCA2* mutation carriers (*BRCA*-positive) versus all non-carriers (*BRCA*-negative) at 2 years, 5 years, and 10 years after diagnosis. A prespecified subgroup analysis of overall survival was done in patients with triple-negative breast cancer. Recruitment was completed in 2008, and long-term follow-up is continuing.

Findings

Between Jan 24, 2000, and Jan 24, 2008, we recruited 2733 women. Genotyping detected a pathogenic *BRCA* mutation in 338 (12%) patients (201 with *BRCA1*, 137 with *BRCA2*). After a median follow-up of 8·2 years (IQR 6·0–9·9), 651 (96%) of 678 deaths were due to breast cancer. There was no significant difference in overall survival between *BRCA*-positive and *BRCA*-negative patients in multivariable analyses at any timepoint (at 2 years: 97·0% [95% CI 94·5–98·4] *vs* 96·6% [95·8–97·3]; at 5 years: 83·8% [79·3–87·5] *vs* 85·0% [83·5–86·4]; at 10 years: 73·4% [67·4–78·5] *vs* 70·1% [67·7–72·3]; hazard ratio [HR] 0·96 [95% CI 0·76–1·22]; p=0·76). Of 558 patients with triple-negative breast cancer, *BRCA* mutation carriers had better overall survival than non-carriers at 2 years (95% [95% CI 89–97] *vs*91% [88–94]; HR 0·59 [95% CI 0·35–0·99]; p=0·047) but not 5 years (81% [73–87] *vs* 74% [70–78]; HR 1·13 [0·70–1·84]; p=0·62) or 10 years (72% [62–80] *vs* 69% [63–74]; HR 2·12 [0·82–5·49]; p= 0·12).

Interpretation

Patients with young-onset breast cancer who carry a *BRCA* mutation have similar survival as non-carriers. However, *BRCA* mutation carriers with triple-negative breast cancer might have a survival advantage during the first few years after diagnosis compared with non-carriers. Decisions about timing of additional surgery aimed at reducing future second primary-cancer risks should take into account patient prognosis associated with the first malignancy and patient preferences.

Funding

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Introduction

Although only 5% of breast cancers are diagnosed in women aged younger than 40 years, a high proportion of deaths from breast cancer occur in this age group, which includes a higher number of patients who carry a pathogenic *BRCA1* or *BRCA2* mutation compared with patients with onset of breast cancer at an older age.[1, 2, 3] Second primary breast cancers are more frequent in high-risk gene carriers, and this higher frequency drives early genetic testing to inform surgical decision making; however, whether a germline *BRCA1* or *BRCA2* mutation has independent prognostic implications after an initial cancer diagnosis is unclear.

BRCA1 loss of function mutations are associated with high-histological-grade, oestrogen-receptor-negative, progesterone-receptor-negative, and HER2-negative (triple negative) breast cancer with a basal-like gene expression profile.4 *BRCA*2-associated breast tumours are usually high-grade, oestrogen-receptor positive, and HER2-negative.5, 6 *BRCA1* mutation carriers have been reported to have enhanced sensitivity to neoadjuvant chemotherapy with cytotoxic drugs.7

Research in context

Evidence before this study

At the initiation of this cohort study (Dec 3, 1999), we searched the PubMed database using the search terms [*BRCA1* OR *BRCA2*] AND [breast cancer or breast neoplasm] AND [survival OR prognosis OR mortality] and identified a few published retrospective studies reporting prognosis in *BRCA* mutation carriers. On Dec 5, 2016, we did another PubMed search for studies of patients who carried a *BRCA1* or *BRCA2* mutation and their prognosis, using the following search terms: "(*BRCA*) AND (survival or prognosis or outcome or mortality) AND (breast neoplasms or breast neoplasm or breast cancer or breast tumour)". Our search was not limited by date or language. We also hand-searched references cited in review papers for additional papers. Previous studies and meta-analyses have reported inconsistent effects of *BRCA1* and *BRCA2* mutations on the outcomes of early breast cancer with better, worse, and similar outcomes for patients with a *BRCA1* or *BRCA2* mutation compared with patients with sporadic breast cancer. These conflicting results might be explained by methodological issues with ascertainment biases introduced by retrospective and selective identification of cases, incomplete genetic testing, small numbers, an absence of adjustment for clinical variables, including treatment, and short follow-up.

Added value of this study

POSH is, to our knowledge, the largest prospective cohort study to compare breast cancer outcomes of patients with a *BRCA1* or *BRCA2* mutation with patients with sporadic cancer. Our findings showed that patients with young-onset breast cancer who have a *BRCA* mutation have a similar overall survival to non-carriers. However, in patients with triple-negative breast cancer, *BRCA* mutation carriers might have a survival advantage compared with non-carriers during the first few years after diagnosis. Our study was strengthened by unbiased recruitment, universal and central genetic testing at the end of the study, and comprehensive pathological, clinical, and follow-up data.

Implications of all the available evidence

Decisions about timing of risk-reducing surgery should take into account primary tumour prognosis and patient preference.

Published studies and meta-analyses have reported better, worse, and similar outcomes for patients with a *BRCA1* or *BRCA2* mutation compared with patients with sporadic breast cancer.[8, 9, 10, 11, 12, 13,14] A comprehensive meta-analysis of 66 studies of breast cancer survival in patients with a *BRCA1* or *BRCA2* mutation compared with non-carrier patients or the general breast cancer population, which assessed study quality as well as outcome data, concluded that "it is not yet possible to draw evidence based conclusions about the association between *BRCA1* [or] *BRCA2* mutation carriership and breast cancer prognosis".[12] We undertook the Prospective Outcomes in Sporadic versus Hereditary breast cancer (POSH) study, the primary aim of which was to determine the effect of inherited *BRCA1* or *BRCA2* mutations on outcomes in patients with young-onset breast cancer.[15, 16]

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Methods

Study design and participants

We did a prospective cohort study at 127 hospitals in the UK (appendix pp 1–2). We recruited young women (aged 18–40 years) diagnosed with primary breast cancer in the UK. Patients were eligible if they were diagnosed with invasive breast cancer aged 40 years or younger. Potential recruits were identified by local breast cancer clinicians, nurses, or research clinical trial practitioners within 12 months of initial diagnosis of invasive breast cancer and the date of diagnosis was defined as the first histological confirmation of invasive breast cancer. All histological subtypes, disease stages (I–IV), comorbidities, and performance statuses were permitted. Patients with a previous invasive malignancy (with the exception of non-melanomatous skin cancer) were excluded.

Written informed consent was obtained from all participants. Ethical approval was granted in 2000 (MREC 00/6/69) and the study was approved for recruitment as part of the UK National Cancer Research Network (NCRN) portfolio in 2002, subsequently the NIHR portfolio. The protocol was published in 2007.[15]

Procedures

All patients received treatment according to local protocols. Details of personal characteristics, tumour pathology, disease stage, and surgical and cytotoxic treatment data were collected from medical records at study entry. Family history was collected by questionnaire. The BOADICEA algorithm, without adjustment for pathological subtype, was used to estimate the probability that an individual might carry a *BRCA1* or *BRCA2* pathogenic variant.[17] Pathology and imaging data were verified with copies of the original reports from sites. For patients treated with neoadjuvant chemotherapy, the initial diameter of the tumour was derived from radiological reports.

The oestrogen-receptor, progesterone-receptor, and HER2-receptor status of the primary tumours was determined from reports of local routine pathology testing of diagnostic core biopsies or tumour resections for clinical use. Hormone-receptor concentrations equivalent to an

Allred score of 3 or more were categorised as positive. Immunohistochemical staining of tissue microarrays in some cases enabled clinical source data for oestrogen-receptor, progesterone-receptor, and HER2-receptor statuses to be corroborated; tissue microarray scores were used to supplement missing datapoints for these receptors.16

DNA for genotyping was extracted from whole blood samples submitted at recruitment. A multiplex amplicon-based library preparation system, Fluidigm Access Array (Fluidigm UK, Cambridge, UK), targeted a panel of breast-cancer-susceptibility genes (including *BRCA1, BRCA2*, and *TP53*) for sequencing using an Illumina HiSeq2500 Next Generation Sequencing Platform (Illumina, Little Chesterford, UK; appendix pp 20–21). Targeted-sequence capture cannot reliably identify large exonic deletions or duplications, therefore multiplex ligation probe analysis was used for patients who met current UK guideline thresholds for clinical genetic testing.17, 18 Predicted protein truncating variants (frameshift, nonsense, and canonical-splice site and large rearrangements) plus other variants (mainly mis-sense) unequivocally defined as pathogenic on the basis of multiple lines of evidence and expert review were assigned to the *BRCA*-mutation carrier group (*BRCA*-positive). All pathogenic variants were confirmed by Sanger sequencing. All other patients, including those with *BRCA1* or *BRCA2* variants of uncertain significance or very low penetrance, were assigned to the same group as no mutation found (*BRCA*-negative) or excluded if they were found to carry a pathogenic variant of *TP53*. For the purposes of this analysis, mutations in other breast cancer genes were not curated.

The study protocol and patient information specified that patients would not be informed of the research genetic-testing results; however, patient information sheets gave information about seeking clinical genetic referral. Clinical referrals for genetic testing were made by the treating physician according to local protocols. Genetic test reports for the study patients generated by UK National Health Service (NHS) diagnostic laboratories were collected as part of the medical record.

Detailed clinical follow-up data, including date and site of disease recurrence, were obtained from medical records at 6 months, 12 months, and annually thereafter, until death or loss to follow-up. Patients were flagged in the NHS medical research information service for automatic notification of date and cause of death.

Outcomes

The primary outcome was overall survival, defined as the time from first diagnosis to death from any cause. The secondary outcomes were distant disease-free survival, defined as time from first diagnosis to first distant disease excluding local (in breast) recurrence.

Statistical analysis

The original study sample size of a minimum of 2000 patients was estimated based on a prevalence of *BRCA1* or *BRCA2* pathogenic mutations of 10%, and an absolute difference in event rate at 2 years between mutation carriers and non-carriers of 10% (20% in mutation carriers compared with 10% in sporadic cases).15 We also considered a prevalence of *BRCA1* or *BRCA2* mutations of 5% and 15%, and larger sample sizes. Good recruitment and data

returns enabled us to continue study recruitment beyond 2000 participants providing sufficient power for multivariable analyses.

We did the statistical analyses according to a prespecified plan (appendix pp 22–31).[19] The analysis population included all eligible patients recruited to the cohort who had available data for the primary tumour and genotyping, were aged 40 years or younger at the date of diagnosis, did not carry a *TP53* gene, and who did not present with metastatic disease at presentation (M1 stage). A prespecified subgroup of the analysis population was patients with triple-negative breast cancer (ie, oestrogen-receptor-negative, HER2-negative, and progesterone-receptor-negative or unknown). All analyses were done for both the overall analysis population and the triple-negative breast cancer subgroup population, unless specified otherwise. Key patient data were described by *BRCA* mutation status, and formal comparisons by *BRCA* mutation status were done using Mann-Whitney tests (for continuous variables) and Pearson $\chi 2$ tests (for categorical variables) for patients with complete data. We used Kaplan-Meier plots to show survival data by *BRCA* status at 2, 5, and 10 years. The 2-year comparison was chosen because this timepoint was specified for the original sample size; the 5-year and 10-year comparisons were chosen because they are commonly used in such studies and are clinically relevant timepoints. Patients who did not have an event were censored at the date of their last follow-up. Hazard ratios (HRs) and 95% CIs for univariable analyses and multivariable analyses (for the primary and secondary outcomes) were calculated using Cox proportional-hazards models, or flexible parametric survival models for those that involved time-varying hazards.[20] For each flexible parametric survival model, varying degrees of freedom for the baseline-hazard rate and time-dependent effect were explored to obtain the best-model fit. All missing data were assumed to be either missing at random or missing completely at random, and censoring was assumed to be non-informative. Prespecified sensitivity analyses included the generation of corresponding complete-case multivariable analysis model results.

Post-hoc sensitivity analyses were done to explore the possible reasons for some of the results in the triple-negative breast cancer group. Additionally, to investigate the degree of potential bias from time of diagnosis to blood draw for genetic testing at registration, a multivariable analysis model adjusting for the time from diagnosis to blood draw was generated accordingly for the analysis population only. We considered if the longer survival of *BRCA* mutation carriers with triple-negative breast cancer could be due to a beneficial effect of risk-reducing surgery in *BRCA* carriers, so we repeated the analysis in this subgroup excluding patients who underwent bilateral mastectomy within the first year after diagnosis. A further sensitivity analysis was done to compare the pattern of improved survival at an early timepoint with apparently worse survival in the long term by excluding patients who developed a new primary breast or ovarian cancer.

We did all analyses with Stata, version 14.2, and multiple imputation was incorporated in the multivariable analyses generated using the mi command.

Role of the funding source

The funders and their representatives had no role in study design, data collection, data analysis, data interpretation, or writing of the report or the decision to submit it for publication. The

corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Results

Between Jan 24, 2000, and Jan 24, 2008, we recruited 3021 eligible women, of whom 2733 (91%) were included in the analysis population, and 288 (9%) were excluded (figure 1; appendix p 11). We included all data received until July 26, 2016. Of 2721 patients for whom presentation was recorded, 45 (2%) were recorded as being enrolled in a surveillance programme, and 33 (1%) were recorded as having screen-detected breast cancer. Screening was offered according to local protocols; national guidelines were not formally established until after recruitment ended.

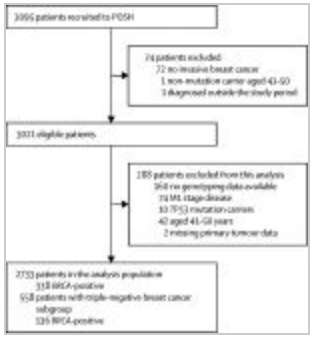

Figure 1

Trial profile

BRCA-positive=patient with *BRCA1* or *BRCA2* pathogenic mutation. Patients were categorised as *BRCA*-negative if no *BRCA* pathogenic mutation was found or they had a *BRCA1* or *BRCA2* variant of uncertain significance or very low penetrance.

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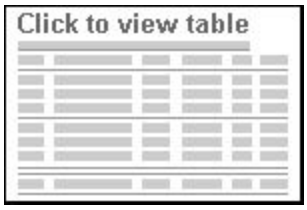
338 (12%) of 2733 patients included in the analysis population had either a *BRCA1* or *BRCA2*mutation, of whom 44 (13%) had large-copy-number variants (appendix pp 3–7). 75 (22%) of 338 patients did not meet current family history or pathology based genetic-testing guidelines.18 Referral for a clinical genetics consultation and *BRCA* testing occurred for 388 patients (14%), of whom 182 (47%) had a pathogenic mutation. Immunohistochemical staining of tissue microarrays in 1336 cases, during 2012 and 2016, enabled clinical source data for oestrogen-receptor, progesterone-receptor, and HER2-receptor statuses to be corroborated.

The median time from breast cancer diagnosis to study registration blood draw was 5·5 months (IQR 3·2–10·7). There were several significant clinicopathological differences between *BRCA*-positive and *BRCA*-negative patients, and between *BRCA1* mutation carriers and *BRCA2* mutation carriers (table 1). The most commonly used chemotherapy regimen was

anthracycline with or without taxanes. Of the 2733 patients in the analysis population, 558 (20%) had triple-negative breast cancer. *BRCA*mutations were identified in 136 (24%) of patients with triple-negative breast cancer, of whom 123 (90%) had a *BRCA1* mutation. Differences in tumour characteristics between *BRCA1* and *BRCA2*mutation carriers were also noted in patients with triple-negative breast cancer (table 2).

Table 1

Baseline characteristics and clinicopathological information for all patients



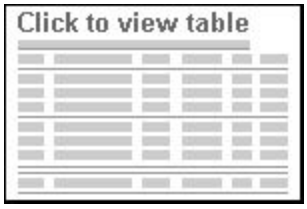
Data are median (IQR, range) or n (%). Patients with missing data were not included in the p value calculation. BMI=body-mass index. CMF=cyclophosphamide plus methotrexate plus fluorouracil.

*Test excluded patients with both *BRCA1* and *BRCA2* mutations. Mann-Whitney tests used for continuous variables and Pearson $\chi 2$ tests for categorical variables, done on patients with complete data.

†Defined as oestrogen-receptor-negative, HER2-negative, and progesterone-receptor-negative or unknown.

Table 2

Baseline characteristics and clinicopathological information for patients with triple-negative breast cancer*



Data are median (IQR, range) or n (%). Patients with missing data were not included in the p value calculation. BMI=body-mass index. CMF=cyclophosphamide plus methotrexate plus fluorouracil.

*Defined as oestrogen-receptor-negative, HER2-negative, and progesterone-receptor-negative or unknown.

†Test excluded patients with both *BRCA1* and *BRCA2* mutations. Mann-Whitney tests used for continuous variables and Pearson χ2-tests for categorical variables, done on patients with complete data.

Median follow-up was 8·2 years (IQR 6·0–9·9); 91 (3%) patients were lost to follow-up. Contralateral breast tumours occurred in 151 (6%) patients: in 37 (18%) of 201 *BRCA1* mutation carriers, 17 (12%) of 137 *BRCA*2 mutation carriers, and 97 (4%) of 2395 *BRCA*-negative patients. Median time to contralateral breast cancer was 3·0 years (IQR 1·5–4·8) in *BRCA*-positive patients and 2·7 years (1·2–5·3) in *BRCA*-negative patients. 752 (28%) women developed a distant recurrence. Of 678 deaths, 651 (96%) were due to breast cancer. Deaths due to non-breast malignancies included six (3%) of 201 new primary cancers in *BRCA1* mutation carriers (three ovarian, one primary peritoneal, one oesophageal, and one pancreatic) and 12 (<1%) of 2395 malignancies in *BRCA*-negative patients (four haematological, three lung, and one each of brain, colorectal, gastric, pancreatic, and sarcoma; appendix p 8). There were no deaths attributed to second primary cancers among *BRCA2* mutation carriers.

Overall survival was 97·0% (95% CI 94·5–98·4) in *BRCA*-positive patients versus 96·6% (95·8–97·3) in *BRCA*-negative patients at 2 years; 83·8% (79·3–87·5) versus 85·0% (83·5–86·4) at 5 years; and 73·4% (67·4–78·5) versus 70·1% (67·7–72·3) at 10 years (figure 2). There was no difference in overall survival between groups either before or after adjusting for known prognostic factors, including adjustments for ethnicity and body-mass index (BMI; univariable analysis negative *vs* positive HR 0·99 [95% CI 0·78–1·24], p=0·90; multivariable analysis HR 0·96 [0·76–1·22], p=0·76). Similar results were noted when comparing distant disease-free survival between *BRCA*-positive and *BRCA*-negative groups (appendix p 12). Additionally, comparison of overall survival in *BRCA*-negative patients versus *BRCA1*or *BRCA2* carriers separately showed similar results (appendix pp 13–14).

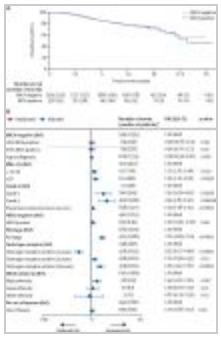


Figure 2

Overall survival for all patients (analysis population) by *BRCA* mutation status

(A) Kaplan-Meier plot and (B) forest plot of corresponding univariable and multivariable hazard ratios. In (B), multivariable analysis was adjusted for age, body-mass index (BMI; kg/m2), grade, tumour size, HER2 status, oestrogen-receptor status, ethnicity, and use of taxane chemotherapy. Groups without a reference were assessed as a continuous variable. The dashed line separates the univariable analysis (UVA) from the multivariable analysis (MVA). Oestrogen-receptor-positive group assessed at 2, 5, and 10 years because the hazard ratio associated with oestrogen-positive status varies with time.16 HR=hazard ratio. *Number of events (number of patients) from complete data obtained before multiple imputation.

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In the subgroup of 558 patients with triple-negative breast cancer, 159 (28%) women developed a distant recurrence, 153 (27%) died, and all deaths were due to breast cancer. The estimated hazard for death after diagnosis of triple-negative breast cancer varied over time (appendix p 32). In the triple-negative breast cancer subgroup, overall survival was significantly better at 2 years for *BRCA*-positive patients than for *BRCA*-negative patients (95% [95% CI 89–97]) *vs* 91% [88–94]; multivariable analysis flexible parametric survival model HR 0·59 [95% CI 0·35–0·99], p=0·047). Overall survival at 5 years was 81% (95% CI 73–87) versus 74% (70–78; multivariable analysis flexible parametric survival model HR 1·13 [95% CI 0·70–1·84], p=0·62); and at 10 years was 72% (62–80) versus 69% (63–74; multivariable analysis flexible parametric survival model HR 2·12 [95% CI 0·82–5·49], p=0·12; figure 3). For distant disease-free survival, however, the difference between *BRCA*-positive and *BRCA*-negative patients was not significant (appendix p 15). Inclusion of time from diagnosis to registration blood draw in multivariable analyses did not affect the results (appendix p 16). For analyses of both the overall population and the subgroup of patients with triple-negative breast cancer, results with imputation were almost identical to complete case results (appendix pp 9–10). Results from tests of proportional hazards are also in the appendix (p 17).

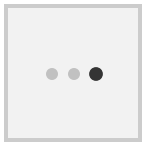

Figure 3

Overall survival for all patients with triple-negative breast cancer* by *BRCA* mutation status

(A) Kaplan-Meier plot and (B) forest plot of corresponding univariable and multivariable hazard ratios. In (B), multivariable analysis was adjusted for age, body-mass index (BMI; kg/m2), grade, tumour size, HER2 status, oestrogen-receptor status, ethnicity, and use of taxane chemotherapy. Groups without a reference were assessed as a continuous variable. The dashed line separates the univariable analyses (UVA) from the multivariable analyses (MVA). HR=hazard ratio. *Number of events (number of patients) from complete data obtained before multiple imputation.

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A post-hoc, multivariable sensitivity analysis of overall survival in patients with triple-negative breast cancer excluding 31 (6%) patients (21 *BRCA*-positive and ten *BRCA*-negative) who underwent bilateral mastectomy within the first year after diagnosis showed a significant difference in overall survival at 2 years for *BRCA*-positive versus *BRCA*-negative patients (95% [95% CI 89–98] *vs* 91% [88–94]; HR 0·52 [95% CI 0·29–0·91], p=0·023). However, there was no significant difference for 5-year overall survival (83% [95% CI 74–89] *vs* 74% [69–78]; HR 0·98 [95% CI 0·58–1·65], p=0·94; appendix p 18). We also repeated the primary analysis in patients with triple-negative breast cancer excluding 37 (7%) patients who developed a new primary breast or ovarian cancer. Overall survival at 10 years for *BRCA*-positive versus *BRCA*-negative patients was 78% (95% CI 69–85) versus 69% (64–74; HR 1·24 [95% CI 0·39–3·96], p=0·73; appendix p 19).

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Discussion

The POSH prospective cohort study showed no significant difference in overall survival or distant disease-free survival between patients carrying a *BRCA1* or *BRCA2* mutation and patients without these mutations after a diagnosis of breast cancer. These results did not vary between unadjusted or adjusted analyses, including adjustments for ethnicity and BMI.21, 22 Following a diagnosis of early breast cancer, *BRCA* mutation carriers are frequently offered additional management options including bilateral mastectomy. Any prognostic implication of carrying a *BRCA* mutation for primary treatment is important to clarify to facilitate clinician and patient decisions around the optimum timing of additional surgery. Furthermore, clinical trials of treatments that are specifically targeted toward *BRCA* mutation carriers might need to take into account any effect of *BRCA* mutational status on primary treatment outcomes.

To our knowledge, this is the largest prospective study to report the prognostic implication of germline *BRCA* mutations and the only one with a preplanned analysis of patients presenting with triple-negative tumours. Our results are in broad agreement with more recent studies,[8], [9], [10], [23] but others have reported conflicting results.[24], [25], [26] Ascertainment biases introduced by retrospective and selective identification of cases, incomplete genetic testing, small numbers, absence of adjustments for clinical variables including treatment, and short follow-up probably explain many discrepancies, although some studies have generally used stronger methods.[11], [12], [13], [14]

The percentage of *BRCA*-positive patients in POSH (12%) was higher than anticipated from historical studies of patients diagnosed aged 40 years and younger, perhaps because of more sensitive mutation-testing options.[1] However, only 14% of all patients had clinical genetic testing. The ratio of patients with *BRCA1* to *BRCA*2 mutations was 1·5 to 1, which is similar to that reported in other large western population-based cohorts.[2], [23] Deaths due to other malignancies were low in frequency in all groups reflecting the young age group; however, causes of deaths in patients who were *BRCA1*-positive included potentially preventable ovarian cancers at age 41–46 years. Bilateral risk-reducing mastectomy is not a necessary part of treating a unilateral breast cancer but unilateral mastectomy might enable breast radiotherapy to be omitted. Discussion about future primary cancer prevention during primary breast cancer treatment should take into account individual circumstances, including the likely tumour prognosis and the physical and psychological implications of more extensive surgery. In the POSH cohort, immediate bilateral mastectomy was not associated with improved survival, although the reported use of risk-reducing surgery was low; bilateral salpingo-oophorectomy was recorded in 32 patients and bilateral mastectomies in 107 patients.[27] This probably reflects the low level of clinical testing at the time of the study. Although risk-reducing bilateral salpingo-oophorectomy is highly effective at reducing ovarian cancer incidence, the risk of primary peritoneal cancer is not reduced and studies indicate that the previously reported effect of this procedure on future breast cancer risk in *BRCA1* and *BRCA2* mutation carriers might have been overestimated because of uncorrected bias.[28]

Our analysis of the 558 patients with triple-negative breast cancer in our cohort showed an intriguing difference in overall survival over the first few years after diagnosis. *BRCA* mutation carriers were less likely to die from early breast cancer than non-carriers. This early survival advantage has also been observed among patients with ovarian cancer who are *BRCA* mutation carriers.[29], [30] If real, this advantage might reflect greater sensitivity of *BRCA*-mutant breast cancers to chemotherapy or the greater visibility of *BRCA*-mutant cancers to host immune attack.[31] One theory that could explain the slight survival advantage for *BRCA* mutation carriers not undergoing immediate bilateral mastectomy is that a major surgical intervention might compromise host immunity at a time when this is particularly important for eradicating micrometastases. This hypothesis would need further exploration due to the small number of patients in this subgroup.

Results from several published studies have suggested that the DNA repair deficiency associated with *BRCA* mutations results in enhanced sensitivity to many chemotherapy agents, particularly higher response rates to platinum-based drugs, have occurred in both metastatic and neoadjuvant settings.[4], [7] Only 13 patients in our cohort were treated with platinum-based

adjuvant regimens for early breast cancer, including one patient with a *BRCA1* mutation and one with *BRCA2*.

Our study illustrates the high breast cancer mortality in this unscreened young population and the effect of known tumour and patient-prognostic characteristics on mortality. Inevitably, there have been substantial changes in the management of *BRCA1* and *BRCA2* mutation carriers since the recruitment period of this study, including the exploration in trials of systemic therapies that exploit *BRCA*-null tumours, including platinum-based drugs and PARP inhibitors. The association of *BRCA*mutations with improved early outcomes related to breast cancer in patients with triple-negative breast cancer has the potential to affect early results from clinical trials. As advanced genomic investigations increasingly become a part of routine oncological care, many patients with breast cancer now learn their *BRCA* mutation status close to the time of diagnosis. In many cancer centres, immediate or post-chemotherapy bilateral mastectomy has become an almost routine recommendation for *BRCA1* and *BRCA2* mutation carriers regardless of the size or focality of the presenting tumour. In the longer term, risk-reducing surgery, particularly for *BRCA1* gene carriers is an appropriate management; in our analysis, the rising hazard for death in *BRCA* carriers over time was negated by removing from the analysis all patients who developed a second new primary breast or ovarian cancer during the follow-up period.

Clinicians need to consider short-term and long-term risks and benefits in discussing risk-reducing bilateral mastectomy with patients. The number of patients with triple-negative breast cancer who had immediate bilateral mastectomy in our cohort was small but our analysis suggests it is unlikely that the early bilateral mastectomy accounted for the early survival advantage in the *BRCA* mutation carriers with triple-negative breast cancer. With modern MRI-based breast screening, we conclude that patients who choose to delay additional surgery for 1 or 2 years until they are psychologically and physically recovered from their cancer treatment can be reassured that this choice is unlikely to lead to any substantial survival disadvantage. The importance of appropriately timed risk-reducing bilateral salpingo-oophorectomy, for *BRCA1* mutation carriers in particular, is clear, but should take plans for further pregnancy into account. Furthermore, risk-reducing bilateral salpingo-oophorectomy in very young women will have negative health consequences as a result of oestrogen deprivation from an early age.

The strengths of the POSH study include the large cohort size, few missing data, and inclusion of patients with young-onset breast cancer, which led to a large number of *BRCA1* and *BRCA2* mutation carriers and a high number of events, ensuring that the study was well powered for the main outcome analysis. Our study minimised many of the biases present in other studies by recruiting patients within the first year after diagnosis from oncology clinics nationally to minimise survival and selection bias and by establishing *BRCA* mutation status for all patients included in the analysis. POSH participants recruited from England represented 23% of the available population during the recruitment period and comparison with cancer registry data confirmed that the POSH cohort is representative of the wider population.16 Comprehensive details of pathology enabled us to do a separate analysis of outcome in patients with triple-negative breast tumours; a unique contribution to this field. We have previously reported the significant and independent prognostic effects of obesity and ethnicity on long-term

outcomes in this young patient group, and this study is the only prospective study to date to include these host factors in multivariable analyses.[21, 22]

Limitations of this study included the non-universal use of multiplex ligation probe analysis; we therefore cannot exclude the possibility that some structural *BRCA* variants were not identified. However, even clinical diagnostic mutation testing is not 100% sensitive because of occult mutations not amenable to current methods (eg, deep intronic splice variants); the investigation of *BRCA1* and *BRCA2* gene sequences in this cohort was more comprehensive than in most other publications. All participants were tested for *TP53* mutations and carriers were excluded from this analysis because of the high risk of non-breast malignancies. We acknowledge that other breast cancer susceptibility gene variants were not excluded; however, these were expected to be very low in frequency or low penetrance, and there is no evidence that they specifically affect prognosis. We had national outcome data up to a median 8·2 years. The treatments given reflected modern oncological practice with almost 90% of patients receiving neoadjuvant or adjuvant chemotherapy; in more than 95% of cases this was an anthracycline or anthracycline plus taxane combination regimen.

Other limitations of this study included restricting the main cohort to patients aged 40 years or younger at the time of diagnosis to enrich for *BRCA* mutation carriers. It is possible that observations in young-onset breast cancer patients might not translate to older ages at diagnosis. Progesterone-receptor testing was not done routinely in many UK centres during the period of recruitment and supplementary data were derived from tissue microarrays rather than full tumour sections. The relevance of triple-negative breast cancer in terms of biology and treatment has only become apparent since the POSH study was designed, so the study was not powered for this as the primary outcome; notably, the only difference in overall survival in this study was seen between mutation carriers and non-carriers in this subgroup. Recommendations for adjuvant treatment in the UK changed over the course of recruitment, with taxanes being recommended for node-positive disease from 2006 and adjuvant trastuzumab for HER2-positive breast cancer routinely available only from 2006. Although we specifically collected information at 5 years about risk-reducing surgery, we cannot exclude the possibility that risk-reducing mastectomy and oophorectomy might have been done at different hospitals from the recruiting cancer centre (eg, at specialist plastic surgery or gynaecological units).

This study confirmed that patients diagnosed with invasive breast cancer aged 18–40 years have a high breast-cancer-specific mortality, and a high proportion are *BRCA1* and *BRCA2* mutation carriers. We found no clear evidence that either *BRCA1* or *BRCA2* germline mutations significantly affect overall survival with breast cancer after adjusting for known prognostic factors. Decisions about timing of risk-reducing surgery should take into account primary tumour prognosis and patient preference. *BRCA* mutation carriers presenting with triple-negative breast cancer might have an improved survival during the first few years after diagnosis compared with non-carriers, although immediate bilateral mastectomy did not account for this advantage. Finally, analysis of early outcome data from trials exploring *BRCA*-deficient tumour treatment in patients with triple-negative breast cancer should be interpreted with caution in view of the possible early survival advantage for *BRCA* mutation carriers.

For more about the POSH study see
http://www.southampton.ac.uk/medicine/research/posh.page

For the BOADICEA algorithm see http://ccge.medschl.cam.ac.uk/boadicea/

Contributors

The study was conceived and designed by DME, PS, and DGA, and planned and executed by DME, DGA, PS, DGE, AMT, PP, LJ, HH, SL, RE, AH, FJG, and SH. Data acquisition, management and curation was done by SG, LTD, ERC, TCM, WJT, RIC, SG-H, BE, LS, and DME. LJ was responsible for central pathology review, and AMD and DFE supervised the final research DNA sequencing. The statistical analysis plan was prepared by TCM, DGA, DME, ERC, and RIC. TCM did the statistical analysis and prepared the figures. DME, ERC, TCM, DGA, and RIC interpreted the data and ERC, TCM, and DME wrote the manuscript. All authors critically reviewed iterations of the manuscript and approved the final draft for submission.

Declaration of interests

ERC declares honoraria from Roche. RIC declares honoraria from GSK and Pfizer. DME declares honoraria from AstraZeneca and Pierre Fabre. All other authors declare no competing interests.

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Supplementary Material

Title	Description	Type	Size
Supplementary appendix		pdf	2.23 MB

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