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Abstract

Session IV of the Second International Colloquium on Cardio-Oncology (Kraków, May 2-4 2018) focussed on the cardiovascular risks of hormonal agents used for the treatment of breast (hormone replacement therapy [HRT]) and prostate (androgen deprivation therapy [ADT]) cancer and continued the theme from Session 3 with a discussion of risk reduction strategies. The discussion then moved to an overview of modern radiation therapy and evolving mechanisms of cardioprotection and the risks and late cardiotoxic effects for patients treated prior to the “modern era” were enumerated stressing the importance of long term follow up of this population.

Keywords	Cardioncology, radiation, hormones, toxicities

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Giorgio Minotti

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REPORT OF SESSION IV OF THE SECOND INTERNATIONAL COLLOQUIUM ON CARDIO-ONCOLOGY, KRAKOW, POLAND, May 3-4, 2018

Treatment specific toxicities

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Abstract

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Session summary

Session IV, chaired by Dr. Steingart (New York, NY) and Jurczak (Krakow, Poland), and involving Drs. Iakobishvili (Tel Aviv, Israel) and Lyon (London, UK) as co-discussant, opened with Dr. Chris Plummer (Newcastle, UK), who reviewed the cardiovascular risks of hormonal agents used for the treatment of breast (hormone replacement therapy [HRT]) and prostate (androgen deprivation therapy [ADT]) cancer and continued the theme from Session 3 with a discussion of risk reduction strategies.

The proportion of cancer patients living 10-years or more after diagnosis has doubled since the 1970s to approximately 50% in adult patients and 78% in breast cancer[1]. This improvement in survival makes it increasingly important to address other competing risks, especially the patients' underlying risk of cardiovascular disease and any increased risk associated with their treatment. Two of the most common cancers in the developed world, breast and prostate, are both significantly influenced by reproductive hormones. Hormonal therapies have been shown to affect tumour cell growth and viability and now represent some of the most effective long-term anti-cancer treatments which are used widely across the world. Reproductive hormones are also known to affect cardiovascular health so it is not surprising that their manipulation can affect patients' overall cardiovascular risks.

Breast cancer shares many risk factors with cardiovascular disease (**Figure 1**), including increasing age, diet, alcohol intake, obesity, physical inactivity and tobacco use[2] and as breast cancer treatments have improved, the risk of death due to cardiovascular disease is now double that from cancer in women aged over 70 years with localised invasive breast cancer[3]. Approximately 70% of breast cancers express estrogen receptors (ER+) and patients with these tumours have an indication for anti-estrogen or aromatase inhibitor (AI) treatment for at least 5 years[4]. Tamoxifen, that interferes with estrogen binding and alters downstream gene expression, acts as a competitive estrogen antagonist in breast tissue and inhibits estrogen dependent tumour growth. Tamoxifen has been the preferred anti-estrogen in clinical practice since the 1980s and increases absolute overall survival at 10-years by 12.9%[5] with no significant increase in cardiovascular mortality.[6,7] In the cardiovascular system, tamoxifen alters lipid metabolism favorably with decreases in total and LDL cholesterol as well as having antiinflammatory and antioxidant effects.

Aromatase inhibitores (AI) also have a major role in breast cancer treatment. More recent trials with AIs, which block the conversion of androgens into estrogens, have shown efficacy and side-effect advantages over tamoxifen and have now become the first-line hormonal treatment.[8] Trials comparing tamoxifen with AIs have shown an association between AI treatment and increased rates of ischaemic heart disease. and this was reflected in ASCO guidelines.[9] However, more recent meta-analyses have demonstrated that when comparing the treatments to placebo, AIs show no increased cardiovascular risk while tamoxifen shows a 33% relative risk reduction compared to placebo or no treatment.[10] The mechanism(s) of this association are not fully understood but tamoxifen use results in a 12% reduction in total and a 20% reduction in LDL cholesterol through inhibition of sterol-D8,7 isomerase and acetyl-coenzyme A acetyltransferase, with anti-inflammatory actions reducing CRP, fibrinogen and cytokine TGF-β.[4,10]

Although rare, breast cancer can also occur in males who also may have hormone repsonsive tumours. There are no randomized control trials of HRT with either tamoxifen or Ais. However, there are 12 non randomized trials that include 312 patients that showed a 5% discontinuation rate due to adverse events with rare CV events that included atrial fibrillation, hypotension and QT prolongation.

Dr. Plummer then shifted to discuss prostate cancer, noting that prostate cancer is the most common cancer to affect men, with over 400,000 new cases each year in Europe, 1 in 8 men being diagnosed with prostate cancer in their lifetimes. The mean age at diagnosis is 71 years and 10 year survival is 84%.[11] Similar to the story with breast cancer in women, men with prostate cancer often have hormone responsive cancers and are known to have a high burden of underlying cardiovascular risk factors at baseline and cardiovascular risk with a published series showing 99 of 100 consecutive patients having a 10-year cardiovascular risk of more than 10%.[12] Observational studies show that in men over 65 years with metastatic prostate cancer, cardiovascular disease is the second most

common cause of death after progressive disease, causing the deaths of 16.3% of men within 5 years.[13] These men need risk stratification then active primary and secondary prevention treatment as recommended in international guidelines.[14]

Androgen deprivation therapy (ADT) improves prognosis in node-positive, hormone responsive prostate cancer[15] and can be delivered in three different ways. Orchiectomy, introduced in the 1940s, results in an immediate and irreversible reduction in testosterone, while GnRH agonists introduced in the 1980s (e.g., leuprorelin) result in an initial increase in lutenising hormone (LH) and testosterone production due to over-stimulation of GnRH receptors before this is suppressed through negative feedback. GnRH antagonist treatment, introduced in 2003 (e.g., abarelix) has an immediate onset of action with rapid reductions in LH and testosterone without the symptomatic “flare” associated with GnRH agonists. Meta-analyses of clinical trial data have shown no increase in cardiovascular disease associated with ADT.[16] However, the men recruited into these trials had lower cardiovascular risk than the overall population and subsequent meta-analyses of large observational studies have shown significantly increased relative risks of myocardial infarction and stroke.[17] Pooled data from 6 phase 3 trials of 2328 men[18] suggest that GnRH antagonists are associated with a lower cardiovascular risk than GnRH agonists but that this benefit appears to be restricted only in men with pre-existing cardiovascular disease. This hypothesis is being tested in an on-going clinical trial.[19] The increased risk associated with ADT is likely to be mediated through standard risk factors, as 3-months treatment with a GnRH agonist is associated with increases in serum insulin, glucose, total and LDL cholesterol, triglycerides and CRP.[20] It is also possible that GnRH agonists have a direct effect on plasma T-cells resulting in higher TNFα and IFNγ, stimulating chronic inflammation within unstable arterial plaques.[21]

For metastatic castration resistent prostate cancer, there are also other mechanisms to reduce circulating androgens. These include anti-androgen drugs (e.g.,

abiraterone), anti-androgen antagonists to the androgen receptor (e.g., enzalutamide) and CYP17P1 inhibitors that interfere with androgen synthesis (e.g., ortenonel). Meta-analyses suggest that these therapies used in prostate cancer are associated with cardiovascular risk factors including hypertension.[22] Finasteride, a 5α-reductase inhibitor of androgen synthesis widely used for symptomatic benefits in bladder outflow obstruction, is not associated with any overall survival benefit.[23]

The focus then shifted to cardiovascular risk reduction. Dr. Plummer stressed the importance of aggressive risk factor modification that includes smoling cessation, diet and exercise and blood pressure control (**Figure 2**). Included in that strategy is lipid management. Dr. Plummer presented intriguing observational studies showing reduced overall and prostate cancer [24, 25] and breast cancer[26]. A number of mechanisms have been proposed[27] that include lowered protein phenylation, reduction in tumour cell proliferation and migration, inhibition of Ras signaling and induction of apoptosis with down regulation of mTOR. To date, there are no definitive randomised controlled trials. In conclusion, Dr. Plummer emphasized that we have excellent evidence-based international guidelines on primary and secondary prevention of cardiovascular events[14] and well-written patient guides to reducing risk.[28]

Dr. Plastaras (Philadelphia, PA) provided the second presentaton of Session IV that was entitled “Cardiac complications of radiation therapy: still a problem?” It is currently widely accepted that radiotherapy has a significant impact on the heart and results in cardiac morbidity and mortality. However, the field of radiation oncology has maintained some skepticism about how this concern should impact their treatments. One of the best known examples of how radiotherapy impacts cardiac endpoints is the treatment of breast cancer. In an earlier era, the design of radiotherapy fields for breast cancer were more focused on treating the target than trying to avoid sensitive organs-at-risk (OARs). This meant that for many left-sided breast cancers, a variably-sized sliver of the heart, which

often included the left ventricle and left anterior descending coronary artery, would have received the full radiation dose. In 2002, a large meta-analysis of 40 clinical trials in early breast cancer was published that had a significant impact on the field[29]. It included studies that randomized to the use of radiotherapy in breast cancer management that were initiated prior to 1990. The main conclusion of that study was that although RT decreased local failure from breast cancer by about 2/3, overall survival at 20 years was barely different. This diminishing of a survival benefit from RT was explained by an in increase in "other mortality." Other studies at the time hinted that this was in part due to the impact on the heart.

A 2005 SEER analysis showed that there was a substantial incidence of ischemic heart disease in breast cancer patients treated with RT, and that this impact was greater in patients treated in older eras (1973-1979 vs. 1980-1984 vs. 1986-1989). In the 1970's cohort, there was a higher incidence of ischemic heart disease (IHD) in patients with left-sided breast cancer compared to right-sided breast cancer (**Figure 3**)[30]. This suggested even more strongly that the adjuvant radiotherapy used in the older era was delivering excess dose to the heart and resulted in an increased risk of coronary artery disease. A seminal moment for many radiation oncologists was the presentation of eye-popping images of cardiac SPECT before and after radiation that showed perfusion defects within the tangential radiation fields, published in 2005[31] (**Figure 4**).

Over time, many radiation oncologists started paying more attention to sparing the heart when possible during breast radiation. The wide-spread adoption of CT-planned radiation allowed for routine contouring of the heart as an avoidance structure, however there was not clear guidance on what the limit should be. In 2013, Darby et al. published an extremely controversial paper that suggested that for each increase in the mean heart dose (MHD) of 1 Gy, there was a relative risk increase of 7.4% for coronary events. This paper was based on using two-dimensional radiation plans superimposed on a "typical"

patient, as patient specific CT data were not available. Despite many potential flaws in the methodology and the attendant criticisms, this paper grabbed the attention of oncologists. Many practitioners adopted very strict limits on radiation dose to the heart, leading to a shift in practice patterns. A follow-up meta-analysis by the Early Breast Cancer Trialists' Collaborative Group reported on cardiac events in patients treated with more "modern era" radiotherapy, namely from 2010 to 2015[31]. They noted that there were detectable differences in the rates of ischemic heart disease in women treated with radiation, and that the risk was related to the calculated MHD. However, the calculated risk of death from IHD associated with 4 Gy MHD was slight compared with known risk factors like smoking or prior ischemic heart disease.. As radiation oncologists treating breast cancer become more aware that the heart is a potential problem, they have been able to take steps to reduce unnecessary radiation dose to the heart and have apparently made significant progressing in limiting excess cardiovascular morbidity and mortality. This awareness that the heart needed to be spared coincided with an explosion of techniques to avoid the heart, which will be discussed in more detail below.

Another "poster child" for radiation-induced cardiac morbidity has been mediastinal lymphoma, in particular Hodgkin lymphoma. Prior to the development of curative multi-agent chemotherapy regimens for Hodgkin lymphoma, this disease was first cured by comprehensive radiotherapy that included radiation of nearly all lymph node regions. At the time, it was thought that the muscle of the heart was radio-resistant, so little regard was paid to heart doses, especially when facing what was at the time an otherwise uniformly fatal disease. As the use of multi-agent chemotherapy regimens spread, there was a slow reduction in the size of radiation fields, which had been considered part of the curative regimen. Until 2013, it was still recommended to use "involved field radiation therapy" (IFRT), which for a mediastinal mass would have treated the entire upper heart by virtue of encompassing the left hilum using the traditional AP-PA radiation fields. In 2002,

Ng and colleagues published an interesting analysis of the causes of death in Hodgkin lymphoma survivors[32]. They noted that within the first decade, Hodgkin lymphoma was the leading cause of death, however, in the next 2 to 3 decades, this risk was eclipsed by second cancer and cardio-pulmonary deaths. Similar to the story with breast cancer, large field radiation added to chemotherapy had a delayed impact on toxicity-related deaths. A randomized trial published in 2012 drove this point home, showing that the use of "extended field" radiation added to ABVD chemotherapy initially benefitted freedom from progression, but after 10 years yielded worse overall survival than chemotherapy-only approaches.[33]

The International Lymphoma Radiation Oncology Group (ILROG) has started advocating for much-reduced radiation volumes after effective chemotherapy using an "involved site radiation therapy" (ISRT) paradigm. Unlike extended field radiation or IFRT, ISRT does not electively radiate previously uninvolved lymph node groups. By harnessing the power of FDG-PET-based chemotherapy response information, radiation oncologists can dramatically reduce the amount of radiated tissue. In parallel to the story with breast cancer, it had been noted that the MHD also correlated with ischemic heart disease[34]. Interestingly, this study also noted that there was an increased risk of coronary heart disease of 7.4% per 1 Gy MHD. These increased risks manifest only after 15 or 20 years following treatment, showing that even "low" doses can cause trouble if the patients live long enough.

This growing respect for the heart has also crossed into treatment for other thoracic malignancies, such as lung cancer, esophageal cancer, and thymomas. It is now routine for radiation oncologists to not only attempt to minimize the mean heart dose, but also to consider dose to particular cardiac substructures, such as the coronary vessels, in particular the left main and left anterior descending coronary arteries.

As radiation oncologists started to appreciate that the heart should be avoided if possible, the differential effects on the sub-tissues of the heart is now being considered. Although the heart is one organ, it is made up of many substructures and tissues, each of which may have a different mechanism of damage from radiation. Furthermore, the fact that radiation causes toxicity on 2 distinct time scales has further added confusion. Acute radiation effects, which are manifested by inhibition of proliferation and compromise rapidly dividing tissues like the skin, mucosa, and bone marrow, are the most obvious radiation side effects. These common side effects typically resolve 2 to 3 weeks after radiation is complete as the rapid turnover tissues, like skin and mucosa, start to rebound. In the heart, there are few “early responding” tissues, the exception being the pericardium. Even so, acute pericarditis is relatively rare, which has been belied the fact that the heart is a radiosensitive organ. The radiosensitivity of the heart manifests primarily as late toxicity. This type of toxicity is characterized by cell loss and fibrosis. In tissues like the breast, it results in skin texture changes, dense scarring and breast fibrosis. Although these late effects can affect breast cosmesis, similar tissue changes in the heart are life-threatening.

Radiated coronary vessels are subject to increased rates of atherosclerosis. Valves become fibrotic and stiff, leading to stenosis and regurgitation. Myocytes are lost, replaced with fibrous tissue that can impact ejection fraction and diastolic filling. The conducting system can be damaged resulting in arrhythmias. The pericardium itself can also develop late effects, such as pericardial constriction and development of effusions. These late effects are well-known to clinicians who have followed patients cured of Hodgkin lymphoma by large field mediastinal radiation. Multi-vessel coronary disease, heart blocks, and valvular dysfunction are the rule rather than the exception.

One tissue that has been less well-characterized is the microvascular system. As was alluded to above, perfusion defects are noted within weeks of radiation. How these

microvascular changes result in some of the above late cardiac radiation toxicities is not well known, but are likely an important mechanism of damage.

Despite the recognition that various substructures can be uniquely sensitive, in 2018 it is still the standard of care to limit the mean heart doses in radiation planning. This means that high doses to a small volume may be equated with large heart volumes getting low doses. There is a growing trend to control radiation doses to the cardiac substructures more carefully, by contouring the various substructures and specifically avoiding them when using highly conformal modern radiation techniques. For mediastinal lymphomas, the distribution of the pre-chemotherapy disease may allow for specific sparing of the coronary vessels and aortic valve, which are likely the most common culprits for life-threatening late cardiac events. It should be noted that other patient-specific factors may influence the impact of cardiac toxicities from radiation. Many studies have noted a synergistic effect of radiation and other established risk factors for coronary artery disease, such as smoking, diabetes, or hypertension. These other comorbidities and risk factors may be considered by radiation oncologists to determine if and how radiation is used in a particular case.

As described above, it took decades for radiation oncologists to even admit that radiating the heart caused problems. The accumulation of data in both breast cancer and lymphomas has finally penetrated the conscience of most practicing radiation oncologists today, but this has been an embarrassingly slow process. Once radiation oncologists admitted that radiating the heart was undesirable, it was actually pretty easy in most cases to contour the heart and try to avoid radiating it. However, in some cases where anatomic factors result in the radiation target to be close to the heart, alternative technological solutions have been implemented to limit the MHD. Although it is common to take pains to limit the MHD, the routine practice of contouring cardiac substructures has not been widely adopted as of 2018. This is in part due to the difficulty in contouring these structures in

non-contrasted CT scans, and in part due to a lack of widely accepted guidelines as to what dose limits these substructures should be subjected.

The first and most important technology that has limited radiation dose to the heart in standard practice has been the use of 3-dimensional radiation planning using CT. The simple step of obtaining a CT scan, contouring the heart, and using 3 dimensional planning has been the most important step for cardiac avoidance. Additionally, advances in other cross-sectional imaging modalities have allowed more precise target definitions, and thus smaller radiation target volumes. This may include FDG-PET and MRI techniques. The impact of functional imaging has been the most significant in the treatment of lymphomas as described above. The evolution of “mantle fields” and extended field radiation for lymphoma to ISRT has been nothing short of revolutionary, reducing doses to sensitive organs by 5-10 fold. The ability to reduce these target volumes is reliant on our confidence in FDG-PET in defining which lymphoma patients have disease that is truly sensitive to chemotherapy. In a parallel story, the breast cancer field has defined which patients may be candidates for “partial breast” irradiation, which also can limit dose to the heart by treating a more limited volume.

Another strategy has been to displace the radiation target relative to the heart. In the treatment of breast cancer, prone positioning can have a dramatic effect on where the target lies with relation to the heart. In particular, patients with large breasts can be challenging to spare the heart. However, having the patient lie on a specially constructed table-top, a pendulous breast can hang away from the chest wall and heart. Alternatively, specialized devices now allow radiation oncologists to deliver radiation only during a precisely calibrated deep breath hold position. A deeply inspired breath has the effect of interposing lung tissue between the chest wall and the heart. This technique can also be used in mediastinal lymphoma, where the heart is displaced inferiorly from a more superior mediastinal target. Many now consider deep inspiratory breath hold as standard for

mediastinal lymphomas, although the availability of this technique may still be limited. A summary of these techniques is seen in **Table 1**.

Advances in radiation planning and delivery have made sparing of the heart and substructures more feasible. Intensity modulated radiation therapy (IMRT) and proton therapy can both allow radiation oncologists to control more precisely how much dose gets to sensitive structures. By “sculpting” the radiation inside the body, we can be stricter about how much radiation dose each organ gets. As mentioned above, radiation oncologists will try to limit the MHD to 3 to 4 Gy for breast cancer and 5 Gy for a mediastinal lymphoma patient. It has not been defined to what dose we should limit valves, but I strive for a mean aortic valve doses of less than 20 Gy for mediastinal lymphomas. Additionally, radiation oncologists attempt to spare the left main and left anterior descending coronary arteries to a mean dose of under 5 Gy and make sure there are no “hot spots” in these vessels. Models using “modern radiation therapy” have shown that these techniques can substantially lower the expected risk of cardiovascular disease in mediastinal lymphoma[35]. In summary, the field of radiation oncology has moved dramatically since the 1990s, where it was common to use 2-dimensional x-rays for simulation, wide treatment fields without regard to the heart, and a reluctance/lack of awareness that cardiac toxicity was important. In 2018, it is standard to use CT simulation often enhanced by other functional cross-sectional imaging for target definition, computer-aided personalized radiation planning, smaller target volumes, conformal radiation including IMRT and proton therapy coupled with cardiac displacement maneuvers.

Although modern cardiac dosimetry is undoubtedly better, it is still wise for radiation oncologists to worry about this potentially life-threatening toxicity. As has been observed in the more curable cancers like Hodgkin lymphoma and breast cancer, if patients live a long time, even modest doses to parts of the heart can manifest decades later. Even with the most sophisticated techniques, some patients still present anatomic challenges that are

difficult to overcome. Although we hope that reduced doses to the heart have clinically meaningful decreases in cardiac events, we don't truly have good long term data on the impact of these techniques. It is still imperative to have to have good multidisciplinary follow-up care. We advocate for a risk-based cardioprotection strategy, where secondary prevention strategies like aggressive lipid-lowering are reserved for patients who have been exposed to high cardiac radiation doses. Dr. Plastaras personally refers all patients that he think will survive who have had any level of heart radiation to a cardio-oncologist for personalized risk-assessment.

We may in the future have good surrogate biomarkers of who is at high risk for radiation-induced cardiac damage, but until then common sense risk reduction, focused on heart-healthy lifestyle choices and aggressive mitigation of cardiac risk factors, should be considered.

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FIGURE LEGENDS

Figure 1. Cardiovascular disease and breast cancer share common risk factors

Figure 2. ABCDE Steps for Heart and Vascular Wellness Following a Prostate Cancer Diagnosis

Fom Guan et al., ref. 28

Figure 3. Ischemic heart disease free survival for patients treated by radiation therapy over different years
From Giorgano et al., ref. 30

Figure 4. Mechanisms of Radiation Therapy Cardiotoxicity: Imaging Acute Perfusion Defects
SPECT images pre-RT and 6 months post-RT: New perfusion defect in the anterior left ventricle under deep tangent border.
Grom Marks et al., ref. 31

Table 1
Modern Techniques to Improve Cardiac RT Dose Exposure

1. Cardiac Displacement Maneuvers
   - Prone positioning
   - Deep inspiratory breath holding
2. Reduction in RT Target Volumes
3. Technological Advances in RT Planning and Delivery
   - Protons vs. photons
   - CT or PET/CT simulation

Figure 1

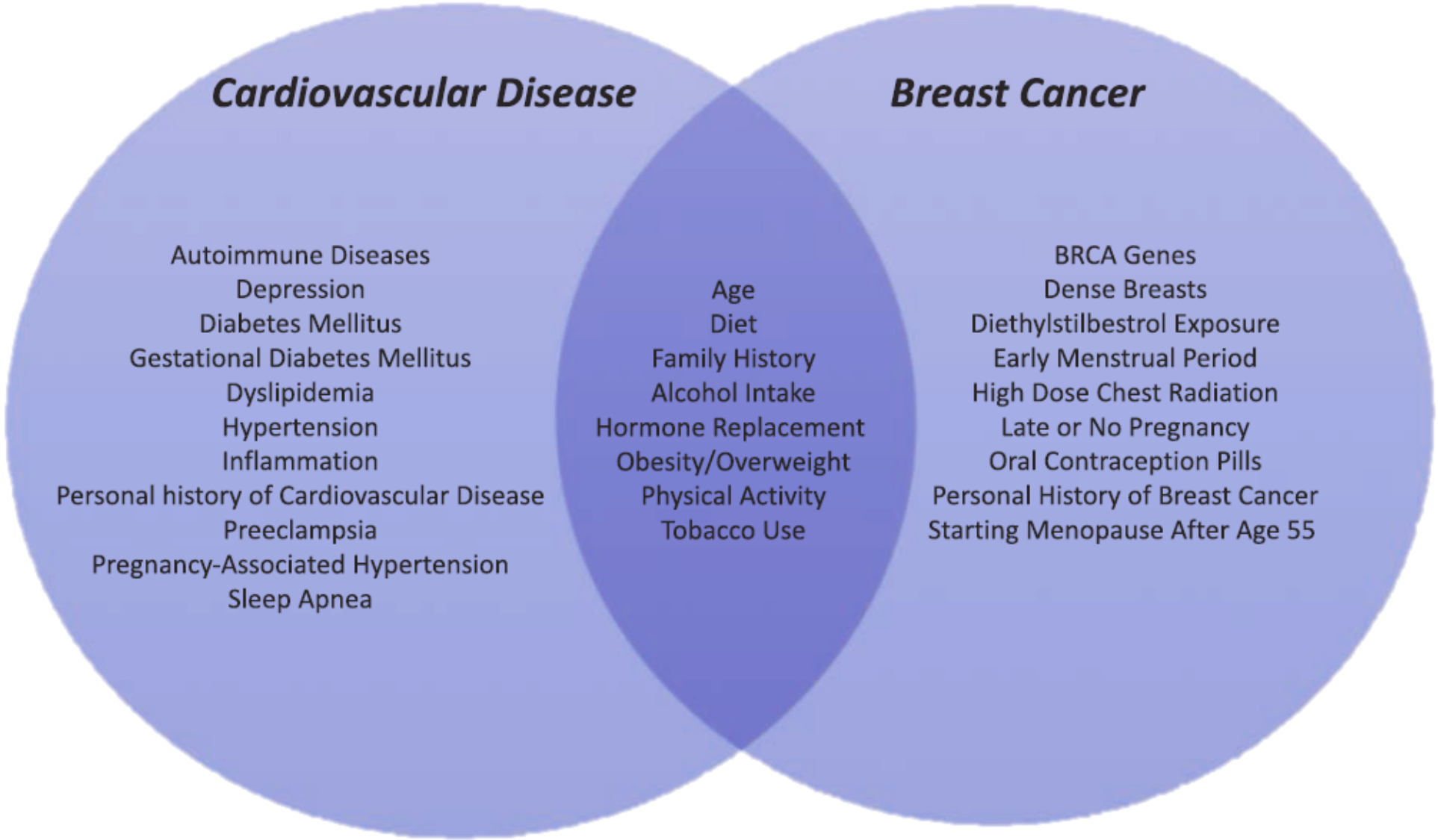

Cardiovascular Disease
Autoimmune Diseases
Depression
Diabetes Mellitus
Gestational Diabetes Mellitus
Dyslipidemia
Hypertension
Inflammation
Personal history of Cardiovascular Disease
Preeclampsia
Pregnancy-Associated Hypertension
Sleep Apnea
Age
Diet
Family History
Alcohol Intake
Hormone Replacement
Obesity/Overweight
Physical Activity
Tobacco Use
Breast Cancer
BRCA Genes
Dense Breasts
Diethylstilbestrol Exposure
Early Menstrual Period
High Dose Chest Radiation
Late or No Pregnancy
Oral Contraception Pills
Personal History of Breast Cancer
Starting Menopause After Age 55

Figure 2

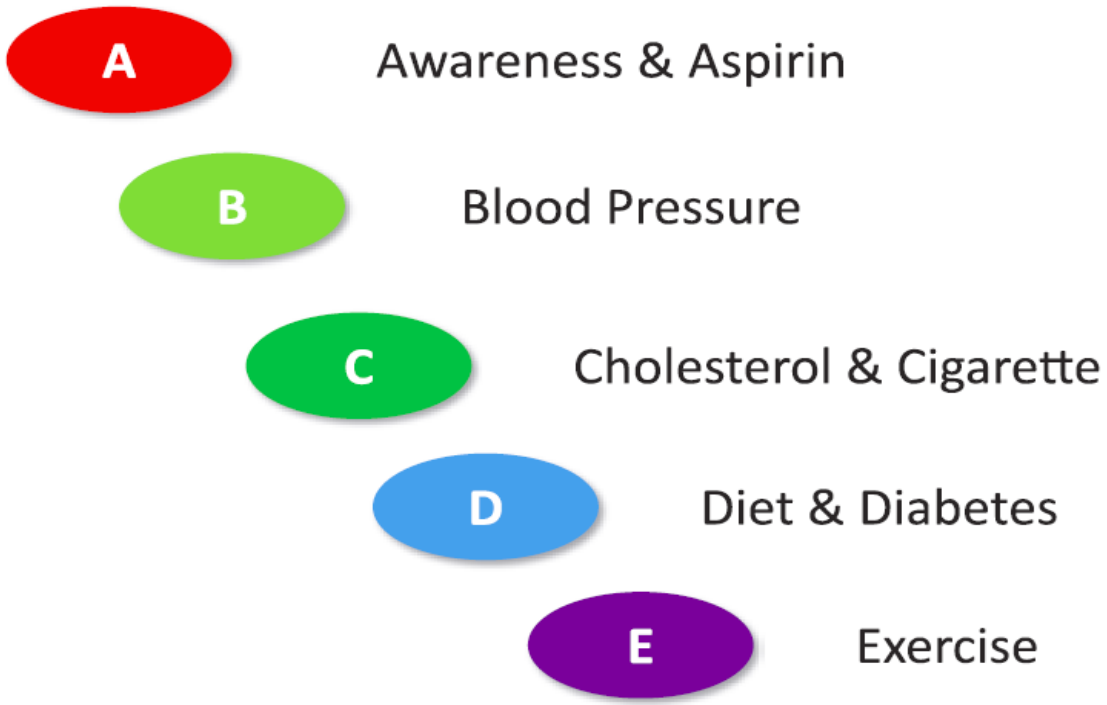
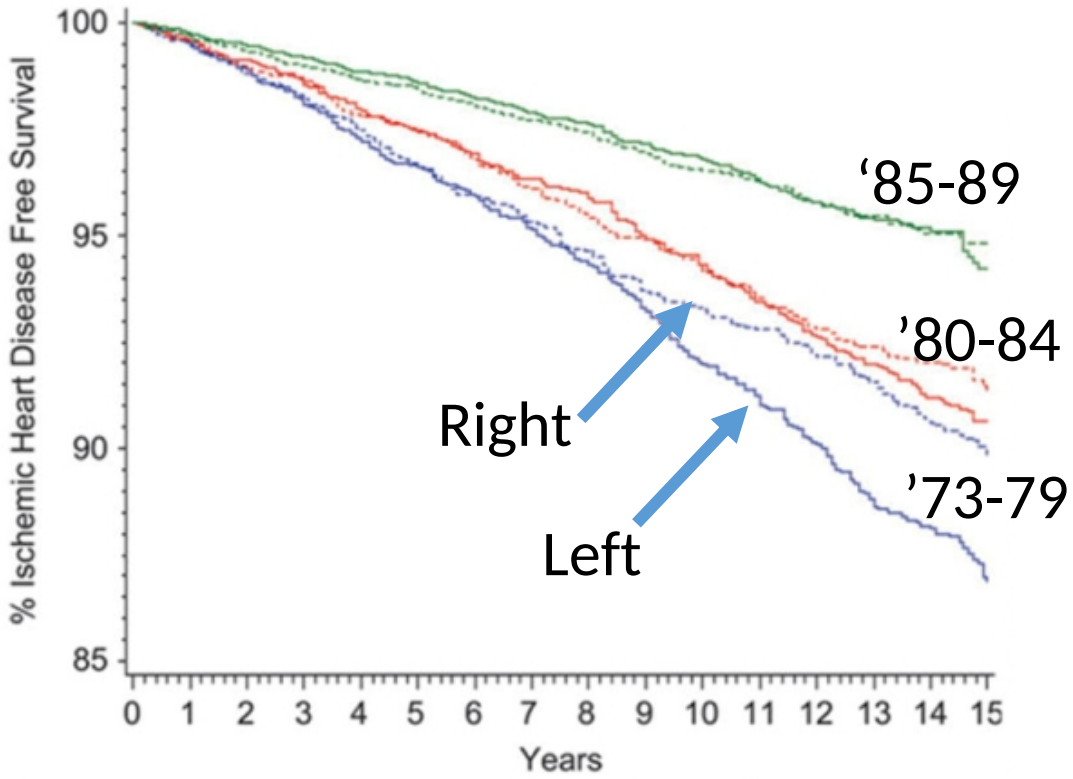
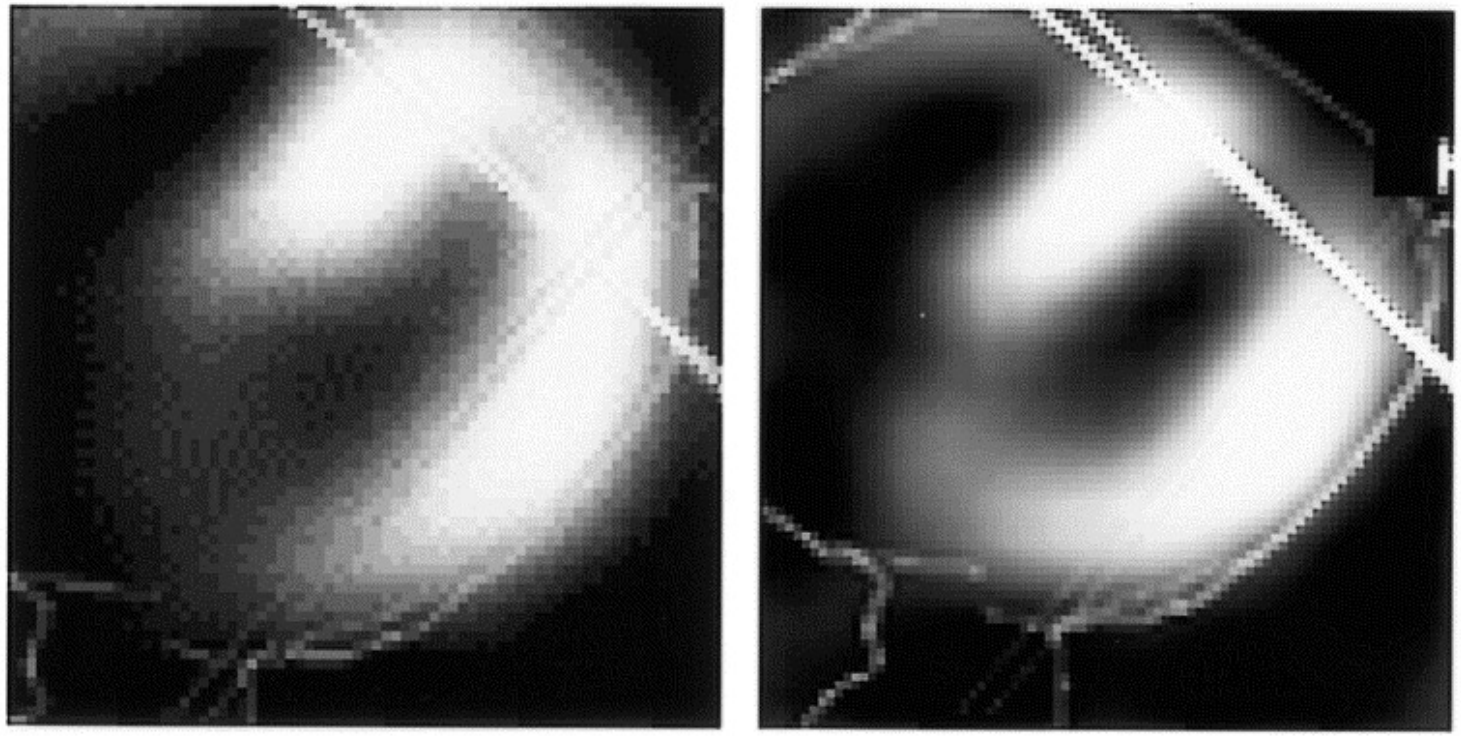

A
Awareness & Aspirin
B
Blood Pressure
C
Cholesterol & Cigarette
D
Diet & Diabetes
E
Exercise

Figure 3



No. of patients at risk		0 year	3 year	6 year	9 year	12 year	15 year
1973-1979	Right	4201	3113	2241	1761	1453	1214
	Left	4451	3305	2384	1885	1523	1272
1980-1984	Right	3131	2539	2044	1676	1425	1232
	Left	3364	2748	2159	1788	1512	1287
1985-1989	Right	5953	5266	4553	4014	2770	507
	Left	6183	5457	4780	4194	2868	533

Figure 4



Pre-RT (a) **Post-RT (b)**

No conflict of interest to declare