Ovarian Cancer: Role of Pelvic Inflammatory Disease in the Development of Cancer

Is Pelvic Inflammatory Disease a contributing risk factor to the development of gynaecological cancers later in life?

For my independent academic project, I will be analysing the long-term health complications associated with Pelvic Inflammatory Disease (PID) and whether having experienced this condition puts one at greater risk of developing gynaecological cancer later life. Cancer has been present in human history since its first documentation in the Edwin Smith Papyrus of 1600 BC, whereby ancient Egyptians claimed there “was no treatment” for the disease, despite previous attempts to cauterize (“burn off” and seal) masses found in breast tissue (Lieberman, 2012). Breast cancer is one of the several cancers primarily affecting women, alongside five types of gynaecological cancer – cervical, ovarian, vaginal, vulval and womb (Royal College of Obstetricians and Gynaecologists, 2019). Scientists have identified a variety risks they believe to be associated with the development of gynecological cancers, particularly the contraction of human papillomavirus (HPV) – a common group of viral strains transmitted through skin-to-skin contact which cause localised infection of the genitals among other areas of the body. Alternatively, exposure to carcinogenic chemical agents (e.g. asbestos, benzene and lead) smoking tobacco, drinking alcohol, malnutrition or obesity, sun damage from UV rays, chronic inflammation and the contraction of certain viruses (e.g. Epstein-Barr, Kaposi's sarcoma-associated herpesvirus (KSHV) and Hepatitis B/C) are also considered contributing risk factors to the development of cancer. For the purpose of this research paper, I will be focusing on the effects of chronic inflammation as a result of PID on the female reproductive system.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) can be defined as an infection of the female upper-genital tract, particularly the womb, fallopian tubes and ovaries (NHS, 2018) which can cause both long-term health complications (e.g. chronic discomfort/bleeding and infertility), and shorter-term but otherwise life-threatening conditions (e.g. septicaemia). PID usually develops as a result of contracting a sexually transmitted infection, most commonly gonorrhoea or chlamydia, which surpasses the cervix and enters the uterus, causing inflammation of the endometrium (tissue lining the womb), fallopian tubes, ovaries and/or peritoneum (tissue lining the abdominal walls). Alternatively, PID can occur because of a natural overgrowth of bacterial flora, cervical damage sustained from childbirth/miscarriage or during open procedures such as an abortion or the insertion of a contraceptive intrauterine device (IUD). Symptoms of PID include; lower abdominal and pelvic pain, difficulty urinating, abnormal bleeding patterns and/or vaginal discharge, fever accompanied by chills, nausea and/or vomiting (Mayo Clinic, 2018). Risk factors for developing PID include having multiple sexual partners, a new sexual partner, a history of STIs, having previously been diagnosed with PID and being under 25 years of age (NHS, 2018).

Cancer

Cancer is an umbrella term used to describe a collection of diseases which form solid masses of tissue known as tumours or reside in the bone marrow (e.g. leukaemia cells) – cancer will often progress if left undetected/untreated, consequently metastasising to vital organs and interrupting key functions necessary for life. Cancer may be ‘malignant’ (with the potential to travel around the blood/lymphatic system and invade different areas of the body) or ‘benign’ (displaying little-to-no regrowth following removal but considered dangerous upon location in the brain (National Cancer Institute at the National Institutes of Health, 2019). Normal cells can specialise to perform a function, for example; mesodermal cells mature into cardiac myocytes during early embryogenesis during differentiation (Sedmera and Thompson, 2011). However, abnormal (cancer) cells are defective; they ignore signals discontinuing growth and inhibit a process known as apoptosis or ‘programmed cell death’ which prompts the death of unnecessary or excess cells (National Cancer Institute at the National Institutes of Health, 2019).

Role of inflammation in the development of cancer

Inflammation is a defence mechanism deployed by the immune system in response to stimuli such as pathogens, injuries caused by foreign objects (e.g. a thorn stuck in a finger) and exposure to chemical or radioactive substances. The site of inflammation may be painful, swollen, hot-to-touch and in advanced stages can poison the blood in a bacterial infection known as septicaemia (Institute for Quality and Efficiency in Health Care, 2010). If left untreated, septic shock (also termed ‘sepsis’) can cause low blood pressure, organ failure, blood clots in the extremities and even death – to prevent this, limbs may be amputated to remove blood clots and damaged tissue, and antibiotics administered both intravenously and in pill form (NHS, 2019).

Sentinel cells can be antigen-presenting cells (APCs) such as Langerhans cells, Kupffer cells, alveolar macrophages, microglia, among other dendritic cells, or can be non-specialised APCs such as mast cells (Nestle and Nickoloff, 2007). Some tissue cells (e.g. epithelial cells and fibroblasts) are also considered sentinel. Sentinel cells act by alerting the immune system to the presence of invaders before releasing chemicals which cause the yellow-coloured substance derived from blood – plasma – to leak into the surrounding area, causing foreign bodies to slow down upon suspension (Anft, 2016). Macrophages release small proteins called cytokines, which are responsible for mediating and regulating immunity, inflammation and haematopoiesis) before B and T lymphocytes collaborate to destroy the invading foreign bodies and tissue damaged by infection (Sino Biological, 2019). Redness and heat are caused by increased blood flow to the affected area, swelling is caused by an excess movement of fluid and white blood cells while pain is caused by chemical-release and compression of nerves.

Acute inflammation caused by PID can cause a collection of purulence known as a tubo-ovarian abscess which, in more serious cases, may require hospitalisation acting upon a referral from a clinician. Professionals may feel the patient is at risk of developing septicaemia, and subsequently drain the abscess during a laparoscopy or an ultrasound procedure. A laparoscope is an operation under general anaesthetic in which a needle-shaped telescope called a laparoscope is inserted through an incision in the umbilicus during keyhole surgery (Hull University Teaching Hospitals, 2019). An ultrasound, sometimes referred to as a sonogram, is a diagnostic imaging technique which uses high-frequency soundwaves to create an image of internal regions of the body – this can be used to monitor pregnancy, diagnose

illness and guide surgeons during surgery (NHS, 2018).

Argument ‘for’

Inflammation is believed to play a pivotal role in tumour progression as cancerous cells are encouraged to metastasise, meaning a secondary malignant growth develops distant from the primary mutation site (e.g. a patient’s ovarian cancer metastasises to the pleural space) (Høilund-Carlsen, 2018). Chronic inflammation is usually caused by an untreated infection, however in some cases can be a result of an abnormal immune response to normal tissue – this is particularly common in women experiencing reoccurring bouts of PID, in which all STI/STD swabs and bloodwork return negative for infection however symptoms are still present. Other conditions, such as ulcerative colitis and Crohn’s disease, act in a similar manner by increasing risk of colon and bowel cancers (National Cancer Institute at the National Institutes of Health, 2015). To highlight the emphasis on chronic inflammation as a contributing risk factor to the development of cancer, the U.S. Preventive Services Task Force (USPSTF) have recently pursued studies recommending anti-inflammatory medications (e.g. aspirin) as a preventative for endometrial cancer.

According to the CAPP2 randomised controlled trial conducted by Burn et al. which involved the daily administration of 600mg of aspirin to individuals with Lynch syndrome – a hereditary disorder known to cause colorectal cancer and endometrial cancer among many others – participants given aspirin showed a 63% reduction in relative risk of developing cancer in comparison to participants who were given a placebo of 30g resistant starch (National Cancer Institute at the National Institutes of Health, 2017). The correlation between reduction in inflammation and reduction in risk of developing endometrial cancer suggests that inflammation caused by PID is a significant contributing risk factor to the development of endometrial cancer; also, that there are preventative measures that can be taken to reduce risk of development.

Argument ‘against’

Arguably, correlations between PID and the development of gynaecological cancers later in life may be entirely coincidental. Complaints caused by symptoms of PID may urge women to see their GP or local sexual health clinic, where cancer may be detected during a Papanicolaou test or ‘smear’ (routine examination where cells from the cervix are swabbed to search for abnormalities which could indicate cancer). An abnormal swab or further testing (e.g. a pelvic exam or biopsy) may detect gynaecological cancer but this does not necessarily mean that PID has caused that cancer to develop. Women at considerably higher risk of having multiple bouts of PID and STIs/STDs (e.g. sex workers) often face several other contributing risk factors – for example, a HIV positive individual or someone who is genetically susceptible to the human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma, is more likely to experience cancer of the skin, mouth and internal organs (NHS, 2017). Other contributing factors include; use of oral contraception and/or fertility drugs, being diabetic, obesity and having a high-fat diet, genetic inclination, smoking, having HIV or HPV, having a weakened immune system (e.g. chemotherapy patients) and exposure to radiation (Northwestern Medicine, 2019). There is no concrete evidence to suggest that a gynaecological cancer has been exclusively caused by PID.

Argument ‘for’

Rudolf Virchow was a German physicist nicknamed “the father of modern pathology” following his discovery of cell theory, in which he declared that not only are all cells a product of pre-existing cells, but that cells are the structural unit of all living things. Virchow described cells as “a number of individual existences” which are mutually dependent on one another, but in such a way that each has its own “special action” which contributes to the overall functioning of the body (Edwards, 2013). His cell theory built upon the findings of French anatomist, Marie-François-Xavier Bichat, who had previously acknowledged the existence of 21 different types of tissue in animals, and that disease could afflict a confined area of the body opposed to a person’s entire being (Underwood, 2019). In 1863, he theorised that the origin of disease was at the site of chronic inflammation (‘chronic irritation theory’), and that resulting tissue injury enhanced cell proliferation; the process in which the number of cells in an organism increases – cell loss caused by death or differentiation is balanced against cell gain caused by cell division to maintain proportionality (Nature International Journal of Science, 2018).

Although cell proliferation does contribute to the growth and eventual metastasis of cancer, Virchow was only partially accurate in his belief that cancer spread in liquid (i.e. leukaemia, lymphoma and myeloma spread through blood/bone marrow) – he otherwise failed to acknowledge the role of metastasis in tumour growth. Additionally, the German Emperor, Kaiser Friedrich III, refused surgery to remove his metastatic laryngeal squamous cell carcinoma after Virchow misdiagnosed it as a benign laryngeal ulceration – the Emperor died as a result, however Virchow avoided penalty after further investigation found his assumption to be reasonable.

Despite previous adversities, Virchow did significantly change the way we see cancer (for example, an enlarged left supraclavicular node is now termed a ‘Virchow’s node’ after he discovered it to be a symptom of gastrointestinal and/or lung malignancy) (Scott & Walter, 2016). Studies conducted by a variety of academic sources following the death of Virchow support the idea that chronic inflammation is a critical component in tumour progression as inflammatory cells orchestrate the microenvironment of tumours, catalysing the processes of invasion, migration and metastasis (Coussens & Werb, 2002). In other words, chronic inflammation encourages cancer to invade tissue, grow rapidly and eventually spread to other parts of the body. In the words of Balkwill and Mantovani’s journal, “Inflammation and cancer: back to Virchow?” published in 2001, “if genetic damage is the “match that lights the fire” of cancer, some types of inflammation may provide the “fuel that feeds the flames”.

Argument ‘against’

It is difficult to find scientific evidence answering the question, ‘Is Pelvic Inflammatory Disease a contributing risk factor to the development of gynaecological cancers later in life?’, as there are few studies challenging the concept. A population-based cohort study, however, conducted by Rasmussen et al. titled ‘Is Pelvic Inflammatory Disease a Risk Factor for Ovarian Cancer?’ found that 5,356 Danish women out of 81,281 (all of which originated from birth cohorts in 1940 – 1970 and had previously been diagnosed with PID) developed ovarian cancer during the 34-year period (1978 – 2012) in which the study took place. Further analysis concluded that PID was not a contributing risk factor to the development of ovarian cancer overall, however analysis of epithelial histotypes did show an increase in risk associated with serous ovarian cancer, also known as a ‘high-grade serous carcinoma’ (Ovcare BC’s Gynaecological Cancer Research Team, 2018). No other histotypes could be associated with increased risk of developing ovarian

cancer.

Despite results being inconclusive, this study did highlight the relevance of inflammation as a contributing risk factor to the development of cancers in general, arguing that inflammation as a result of infection is thought to be the cause of 25% of all cancer cases worldwide (with reference to the work of Hussain & Harris, 2007). This study has a variety of strengths, especially because of its position as a cohort study; the study promotes validity as research measures what it initially intended to measure, includes both objective and subjective data and is representative of a large, diverse population. It also analyses multiple exposures, such as women who have never been diagnosed PID, have already experienced ovarian cancer (including serous, mucinous, endometrioid, clear cell among other epithelial histotypes) and have even had a unilateral or bilateral oophorectomy (removal of the ovary and corresponding fallopian tube) (Mayo Clinic, 2017).

This study was likely to have been costly and time consuming having been conducted over a 34-year period and could potentially be biased due to a loss of follow-up data or ineligibility (e.g. caused by mortality or inability to contact participants). The study also could not account for women who had experienced PID outside of a hospital setting or outpatient clinics before 1995, meaning that only the most severe cases were documented and included in the study (Rasmussen et al., 2017). Additionally, the onset of PID in participants could have been a misinterpretation of early symptoms of ovarian cancer, opposed to a contributing risk factor to its development later in life. The study also does not account for other important contributing risk factors, such as menopausal status and infertility (Rasmussen et al., 2017). Conclusively, evidence was not considered reliable enough to identify PID as a contributing risk factor to the development of ovarian cancer later in life, despite a significant correlation between previous episodes of PID and future ovarian cancer diagnosis.

My Survey Report And Results

I conducted a survey titled ‘Factors Influencing Risky Sexual Behaviour and the Consequences’ using Survey Monkey to assess correlations between usage of barrier methods (particularly condoms), the regularity of sexual activity/sexual partners and contraction rates of STIs/STDs, alongside longer-term health complications such as chronic PID, infertility and discomfort. The survey was shared on my personal Facebook and ‘Girlsmouth’, a women-only Facebook group with 160,000 members, and included a disclaimer acknowledging the sensitive nature of the topic, anonymity of data collected and offering further resources regarding sexual health.

Participants were asked to identify their sex, age bracket (18-24, 25-34, 35-44, 45-54, 55-64, 65+), sexual orientation, relationship status, number of sexual partners within the previous 12 months (0, 1, 2-4, 5-9, 10+) and preferred method of contraception; pill (combined or progesterone-only), patch, implant (e.g. Nexplanon), injection (e.g. Depo-Provera, Sayana Press or Noristerat), intrauterine device (e.g. the coil), male/female condom and sterilisation (female tubal ligation/male vasectomy). Particularly sensitive questions, such as biological sex, sexual orientation and reasoning behind not choosing to use contraception had an additional option of ‘other’ or ‘prefer not to say’ for ethical reasons.

My findings

My survey consisted of 10 questions, took place over a period of 5 days and involved 100 respondents in which there was a 100% completion rate. Results showed a positive correlation between higher numbers of sexual partners within the previous 12 months and contraction rates of STIs/STDs, particularly chlamydia (10%), herpes type 1 and 2 (3%) and genital warts (2%). Of the 7 participants who had contracted an STI/STD, particularly gonorrhoea and chlamydia, 4 developed Pelvic Inflammatory Disease (PID) as a result – this data suggests that not only do individuals with multiple sexual partners have a higher risk of contracting an STI/STD, but that doing so has the potential to cause long-lasting health complications. Additionally, of the 7 participants who had contracted an STI/STD, 1 experienced chronic discomfort which is recognised as an inflammatory response.

Strengths of my research

The quantitative nature of this survey meant that I could examine the relationship between multiple variables, notably contraction rates of STI's/STD's and long-lasting health complications; this made identifying cause and effect relationships possible. I found data to be relatively easy to analyse due to high levels of engagement in which only a small quantity of the population 'opted-out' of answering questions by responding with 'prefer not to say' or skipping the question altogether. This study was cost-effective because it was formatted through the free online website, Survey Monkey, and provided a readily-available population of subjects with varying characteristics and backgrounds via the share button.

Limitations of my research

However, this survey had several limitations – for example, relative secondary data was not available as the media I used to format my survey did not allow this, and my questions were 'closed-ended', rendering them inflexible and at risk of low validity (BetterThesis, 2019). Alternately, due to social stigma surrounding the topic of STIs/STDs, participants may have been inclined to answer questions in a manner thought to be viewed more favourably by others. The tendency to give positive self-description, termed 'social desirability bias' or 'socially desirable responding (SDR)', would explain why 87% of participants reported never having contracted an STI/STD, despite several participants declaring multiple new sexual partners and failures in consistent condom use. Questions also could have been interpreted differently by different participants, for example, "Which of the following best describes your relationship status?" could be difficult to answer if a participant is currently in the process of a divorce, experiencing complications with their partner or part of a polyamorous relationship. It is also possible to misfire when answering questions, for example, the option "I have never had a sexually transmitted infection/disease" is available on two occasions – 86 respondents chose this option during question 9, and 88 during question 10, rendering data unreliable.

What would I change next time? And conclusion

If I was to repeat this research, I would carefully consider generalisation when conducting my study; for example, a fraction of the population having had 10+ sexual partners in the previous 12 months and inconsistently practising condom use does not necessarily mean that these participants are more likely to contract an STI/STD or experience long lasting health complications than those who have little-to-no sexual partners and consistently practise condom use. For instance, adult actors in the pornography industry must perform in compliance with

strict UK legislation which states that a full screening for chlamydia, gonorrhoea, syphilis and HIV must be carried out every 2 weeks to prevent the spread of STIs/STDs (BBC, 2012). Therefore, despite having a higher rate of regular (and often unprotected) sexual partners, rates of transmission are considerably lower than non-sex workers because performers are expected to be conscious and proactive in their approach to sexual health.